

THE
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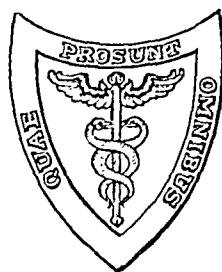
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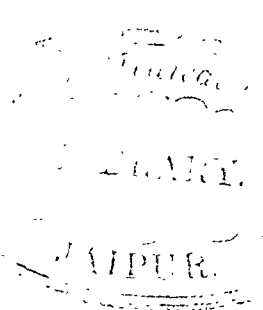
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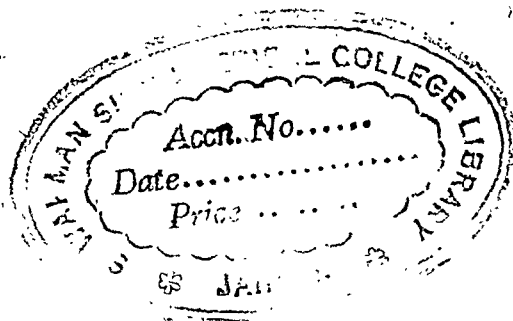


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THE
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JULY, 1932

ORIGINAL ARTICLES.

THE EFFECT OF LIVER THERAPY ON THE NEUROLOGIC
MANIFESTATIONS OF PERNICIOUS ANEMIA.

BY BENJAMIN M. BAKER, JR., M.D.,

JAMES BORDLEY III, M.D.,

AND

WARFIELD T. LONGCOPE, M.D.,

BALTIMORE.

(From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital.)

SINCE the introduction by Minot and Murphy¹ of liver in the treatment of pernicious anemia, there has been considerable discussion in the literature as to the influence of the liver diet on the progress and the prevention of the nervous symptoms in this affection. The intensive study which has been devoted to this subject has, moreover, given rise to a reconsideration of the form and situation of the lesions in the central nervous system, and the relation of subacute combined degeneration to the anemia itself.

It is a generally accepted fact that symptoms referable to alterations in the nervous system, occur in a very large percentage of cases of pernicious anemia. In Woltman's² series of 150 cases they were present in 80.6 per cent. Schilling³ considers, for practical purposes, that some part of the nervous system is affected in practically all cases of pernicious anemia. This cannot be interpreted to mean that an extensive "Funicular myelitis" or myelosis, as Henneberg⁴ terms it, occurs invariably in every case of pernicious anemia, but signifies that such slight symptoms as numbness and tingling in the

extremities should be ascribed to some change in the nervous system. According to Simons, Zador and Bielschowsky⁵ the glossitis is to be attributed to, or at least is associated with, alterations in the peripheral nerves and should therefore be included among the most common manifestations of injury to the nervous system.

Minot and Murphy⁶ suggested, in their report on the treatment of their first 105 cases of pernicious anemia by liver, that a favorable effect on the course of the nervous symptoms might be observed. Since then there has been much discussion as to how much effect, if any, liver diet has upon the nervous symptoms. Ordway and Gorham,⁷ McAlpin,⁸ Starr,⁹ Seyderhelm,¹⁰ Naegeli¹¹ and Smithburn and Zerfas¹² have observed slight if any benefit upon the progress of the nervous symptoms. Seyderhelm¹⁰ goes so far as to say that the liver diet has no effect on the symptoms referable to the combined degeneration and that in spite of relief from anemia the disease progresses to a "pernicious myeloencephalotoxosis."

On the other hand, there are published descriptions of an increasing number of isolated cases, together with several reports of fairly large series of cases, which show that the use of liver, in adequate dosage and administered over a sufficiently long period of time, may result in both symptomatic and objective improvement in at least some of the symptoms and signs due to involvement of the nervous system in pernicious anemia. Lottig,¹³ from an experience with 5 cases of combined degeneration, was favorably impressed by the possibilities of benefit from liver therapy. Schilling,¹⁴ reviewing 80 cases of pernicious anemia treated by liver, states, without detail, that remarkable improvement in nervous symptoms frequently occurs. Ungley and Suzman¹⁵ review 61 cases of pernicious anemia, all of which showed nervous symptoms, and 30 of which were treated by liver. In 63.9 per cent the first symptom of the disease was one suggesting involvement of the nervous system. The symptoms were referable, they believed, to lesions in the posterior columns, the lateral pyramidal tracts or to combined degenerations of the spinal cord. Of the 30 cases treated with liver, 17 improved, 8 were unimproved, and 5 died. Of 31 cases not treated by liver, none improved, 3 were unimproved and 28 died. Eight of the 17 improved cases were at work. Numbness and tingling, present in all 30 cases, disappeared completely in 10. Girdle sensation disappeared; incoördination and ataxia disappeared in 10 cases. Changes in cutaneous sensation, present in 12, became normal in 8. Astereognosis, present in 2, disappeared in 1. The knee jerks remained unchanged. Babinski reactions, present in 9, disappeared in 5. Disturbances of micturition, present in 7, disappeared in 6.

Richardson¹⁶ states that improvement has occurred when the symptoms were tabetic in type, but that when the spastic form of combined degeneration occurred, improvement was not observed; and that, in spite of a satisfactory increase in hemoglobin and red

blood cells, the symptoms and signs might progress rapidly. Davidson, McCrie and Gulland,¹⁷ Henning^{17a} and McAlpin⁸ have come to much the same conclusion.

In a recent article (1930) Sturgis, Isaacs and Riddle¹⁸ have apparently modified somewhat their original view, and state that, in their series of cases treated by liver, not only the slight neurologic manifestations but sometimes symptoms and signs, that are apparently due to extensive funicular degeneration, may improve to a remarkable degree. Farquharson and Graham¹⁹ report the results of treatment of 50 cases of pernicious anemia, 18 of which had well-marked symptoms and signs of subacute combined degeneration. Ten of these 18 cases showed marked improvement, 4 were definitely improved but still incapacitated for work; in 2 the process was arrested or slightly improved; and 2 died, 1 of pneumonia, the other after leaving the hospital, probably of myocardial failure. In no instance did they note an increase in the nervous manifestations when adequate amounts of liver were given, with the possible exception of 2 cases in which contracture of the legs became more marked. The improvement which they noted occurred in such symptoms and signs as numbness and tingling, loss of vibratory sense, ataxia, changes in cutaneous sensibility, loss of knee jerks; extensor plantar response; disturbances in micturition and laryngeal ataxia. They state that the greatest improvement occurred from 2 to 6 months after the liver diet had been started; that the patients with recent involvement of the nervous system improved most; that on inadequate amounts of liver or with the irregular administration of liver relapse occurred with rapid progression of symptoms, and that the average daily dose of liver required was 250 gm.

Sturgis and Isaacs²⁰ have found that whole pig's stomach, dried and ground, is very effective in producing a remission in pernicious anemia, and it is important to know whether this form of therapy, as well as liver or liver extract, is capable of arresting or affecting beneficially the nervous manifestations of the disease. So far, there is little information on this point, though Sturgis and Isaacs state that the effect upon the clinical symptoms cannot be differentiated from that produced by liver. Conner²¹ makes the same statement and reports the disappearance or improvement of numbness and tingling, weakness and mild psychic disturbances.

In a previous note²² we have referred to the alterations that have been brought about in the neurologic symptoms in pernicious anemia as a result of treatment with liver or liver extract. In a series of 44 cases there were 39 who showed some definite evidence of involvement of the nervous system. Among these we have included cases with numbness and tingling in the extremities, and with diminished or lost vibratory sense. In 8 of the 39 cases there were definite symptoms and signs of outspoken combined degeneration. Of the total 39 cases some improvement was noted in 24 (61.5

per cent), no improvement could be detected in 14 (36 per cent), and 1 patient grew worse. The detailed list of the symptoms and signs observed in these patients, with the figures giving the total number of symptoms and signs that improved, that remained unimproved or grew worse, are given in the following tables. Among these cases were to be found most of the common symptoms and signs referable to disease of the nervous system in pernicious anemia; and in addition some manifestations that are decidedly rare. Numbness and tingling occurred in 34, absent or diminished vibratory sense in 32, weakness in 44, ataxia in 19, Romberg's sign in 15, spasticity in 9, hyperreflexia in 7, hyporeflexia in 8, plantar extension in 9, disturbed cutaneous sensibility in 7, sphincter disturbance in 6, psychic disturbance in 7, loss of potentia in 5, paralysis of diaphragm in 1.

Though all of the patients have been treated with liver, or a combination of liver and liver extract in large amounts, it has not been possible to follow all of them with sufficient accuracy or for a long enough period of time to determine what the final result of this treatment has been. The importance of the duration of treatment will become apparent in two of the succeeding tables. Table 1 illustrates the results obtained in the entire group of 44 patients who were treated for periods varying from 2 weeks to 40 months.

TABLE 1.—THE OCCURRENCE OF SIGNS AND SYMPTOMS OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN 44 CASES OF PERNICIOUS ANEMIA TREATED BY LIVER OR LIVER EXTRACT FOR PERIODS VARYING FROM 2 WEEKS TO 40 MONTHS AND THE RESULTS OBTAINED.

	Cases.	Well.	Im- proved.	Sta- tion- ary.	Worse.	Not fol- lowed.
Numbness and tingling	34	6	11	12	2	3
Absent vibratory sense	16	1	1	10	..	4
Diminished vibratory sense	16	2	3	6	1	4
Weakness	44	4	36	3	1	
Ataxia	19	1	12	2	1	3
Romberg's sign	15	2	3	8	..	2
Disturbed position sense	14	1	2	8	..	3
Spasticity	9	1	1	5	..	2
Increased reflexes	7	..	1	2	..	4
Diminished reflexes	8	1	1	3	..	3
Plantar extension	9	2	..	5	..	2
Disturbed cutaneous sensibility	7	2	1	3	..	1
Sphincter disturbance	6	2	3	1		
Psychic disturbance	7	4	2	1
Loss of potentia*	5	3	1	1		
Total observations	216	32	78	69	5	32

34 males; 10 females.

* Data available on only 5 cases.

Table 2 illustrates the results obtained in 23 patients selected from the entire group, who were treated for more than 6 months. Here the improvement in signs and symptoms of involvement of the nervous system has increased considerably and amounts to 55.17 per cent. This rather slow improvement has been noted repeatedly.

TABLE 2.—RESULTS OBTAINED IN 23 PATIENTS TREATED BY LIVER OR LIVER EXTRACT FOR MORE THAN 6 MONTHS.

	Cases.	Improved.	Unimproved.	Not followed.
Numbness and tingling	18	10	7	1
Absent vibratory sense	9	2	6	1
Diminished vibratory sense	8	3	4	1
Weakness	23	22	1	
Ataxia	9	7	2	
Romberg's sign	7	3	4	
Disturbed position sense	8	4	4	
Spasticity	4	1	3	
Increased reflexes	4	2	1	1
Diminished reflexes	4	3	1	
Plantar extension	4	3	1	
Disturbed cutaneous sensibility	5	3	2	
Sphincter disturbance	3	3		
Psychic disturbance	4	4		
Total observations	110	70	36	4

Excluding weakness, signs and symptoms improved, 55.17 per cent.

Excluding weakness, signs and symptoms unimproved, 40.23 per cent.

Excluding weakness, signs and symptoms not followed, 4.60 per cent.

Table 3 shows the results obtained from treatment of less than 6 months' duration, and it is to be noted that the improvement in the signs and symptoms is much less striking than is illustrated in Table 2, and amounts to only 31.25 per cent.

TABLE 3.—RESULTS OBTAINED IN 21 PATIENTS TREATED BY LIVER OR LIVER EXTRACT FOR LESS THAN 6 MONTHS.

	Cases.	Improved.	Unimproved.	Not followed.
Numbness and tingling	16	7	7	2
Absent vibratory sense	7	..	7	
Diminished vibratory sense	8	2	2	4
Weakness	21	19	2	
Ataxia	10	7	2	1
Romberg's sign	8	3	4	1
Disturbed position sense	6	..	6	
Spasticity	5	2	3	
Increased reflexes	3	..	1	2
Diminished reflexes	4	..	2	2
Plantar extension	5	..	5	
Disturbed cutaneous sensibility	2	..	1	1
Sphincter disturbance	3	2	1	
Psychic disturbance	3	2	1	
Total observations	101	44	44	13

Excluding weakness, signs and symptoms improved, 31.25 per cent.

Excluding weakness, signs and symptoms unimproved, 52.5 per cent.

Excluding weakness, signs and symptoms not followed, 16.25 per cent.

Table 4 shows the results obtained in 8 cases (selected from those in Table 2) of outspoken combined degeneration which have been treated for 10 months or more. The definite improvement or disappearance of such objective signs as spasticity, plantar extension, and changes in cutaneous sensibility must lead to the conclusion that some actual change has taken place in the lesions of the nervous

system. Of the signs and symptoms exhibited by the 8 patients in this group, 58.9 per cent showed improvement.

TABLE 4.—RESULTS OBTAINED IN 8 CASES OF OUTSPOKEN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD TREATED BY LIVER OR LIVER EXTRACT FOR MORE THAN 10 MONTHS.

	Cases.	Improved.	Unimproved.	Not followed.
Numbness and tingling	8	4	4	
Absent vibratory sense	6	2	3	1
Diminished vibratory sense	2	..	2	
Ataxia	8	6	2	
Romberg's sign	7	4	3	
Position sense	6	4	2	
Spasticity	4	1	3	
Increased reflexes	3	2	1	
Decreased reflexes	3	2	1	
Babinski	2	2		
Disturbed cutaneous sensibility	4	3	1	
Sphincter disturbance	3	3		
Total observations	56	33	22	1

Improved, 58.93 per cent.

Unimproved, 39.28 per cent.

Another point which has impressed us is the rapid return of symptoms and signs when the liver is reduced in amount or is actually omitted. This has occurred in several instances, and we have noted a second period of improvement when proper amounts of liver were again added to the diet. We have further observed the most favorable outcome in those patients who have conscientiously consumed large quantities of liver and liver extract daily. It has seemed that 400 gm. of liver or its equivalent daily was essential in some instances, and many patients have taken more.

It is important to know whether the improvement in neurologic symptoms can be correlated with the rise in the blood count. In the following table the improved and unimproved cases are charted against the blood count when originally seen, and the blood count when the patient was last seen.

TABLE 5.—RESULTS IN RELATION TO RED BLOOD CELL COUNTS.

		Original R. B. C. Counts.						
		Millions.						
No.	Condition.	0-1.	1-1.5.	1.5-2.	2-2.5.	2.5-3.	3+.	Total.
24	Improved	2	8	5	5	1	3	
14	Unimproved	2	2	3	3	..	4	
1	Worse	1					
<hr/>		<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>
Total 39		4	11	8	8	1	7	39
		Last R. B. C. Counts.						
		Millions.						
No.	Condition.	1.5-2.	2-2.5.	2.5-3.	3-3.5.	3.5-4.	4-4.5.	4.5-5. 5+ Total.
24	Improved		1	..	3	4	10 6
14	Unimproved	2		1	5	3	1	1 1
1	Worse	1	
<hr/>		<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>
Total 39		2	2	5	6	6	11	7 39

From the above table it can be noted that of the 24 cases that improved, the red blood corpuscles, after treatment, were above 4 million in 20, above 4.5 million in 16, and actually above 5 million in 6. Of the 15 cases that did not improve the red blood corpuscles failed to react 4 million in 11 instances and were above 4.5 million in only 3 instances. It has seemed, therefore, that although the correlation between improvement in neurologic symptoms and marked increase in red blood corpuscles is not absolute, yet it is noticeable that pronounced improvement is usually associated with a high red blood cell count. This, however, may not be true in isolated instances.

In order to illustrate the exact course of the disease, the following cases are reported in brief:

Case Reports. CASE 1.—E. A., Unit No. 29913, a white male, aged 64 years, a farmer, was admitted to the Johns Hopkins Hospital, March 7, 1930, and discharged May 18, 1930. He complained of paralysis of the feet since Christmas, 1929. The family history was unimportant, and the past history revealed that he had enjoyed singularly good health.

He dated the present illness to June, 1929, when after a fall, cramplike pains appeared in the feet and legs. Immediately after this accident, he noted progressive weakness and a difficulty in controlling his feet, saying that he could not tell where they were unless he looked down at the ground to see. By August, he was unable to walk without a cane, and "prickly-numb" sensations had appeared in both feet. By November, he was unable to walk without assistance, and in December his disability had become so great that he was forced to take to bed. In February, 1930, incontinence of urine and feces set in.

On *physical examination* he was found to be an emaciated, pale, large-framed man with marked atrophy of the papillae of the tongue and with complete adentia. The chief points of interest in the examination were referable to the central nervous system. The skeletal muscles were extremely wasted and flabby, and there was a flaccid paralysis of both lower extremities. Strength was relatively good in the arms and hands. There was complete paralysis of the diaphragm which was confirmed by fluoroscopic examination. There was complete loss of sense of position in the feet, ankles, and knees, and there was great impairment in appreciating touch, pain and temperature stimuli as far as the fourth dorsal segment. Below the anterior superior iliac spines, vibratory sense was almost completely lost. The abdominal reflexes, knee kicks, and ankle jerks were completely absent, and there was a bilateral, positive Babinski sign. He was both irritable and depressed.

Blood. R. B. C., 2,540,000 per c.mm.; Hb., 64 per cent; W. B. C., 7400 per c.mm. Examination of the smear revealed moderate anisocytosis and poikilocytosis. The urine showed evidences of an extensive urinary tract infection. Even after histamin, the stomach secreted no hydrochloric acid.

On March 9, 6 vials daily of Lilly's liver extract were started, and on March 18, the reticulocytes reached a peak of 6.5 per cent.

Course. At the time of discharge, the blood count had risen to R. B. C., 5,170,000 per c.mm.; Hb., 104 per cent, and W. B. C., 7800 per c.mm. The weakness had improved considerably, so that he could flex both knees and move both legs about in bed. Normal diaphragmatic movements had returned, and the rectal incontinence was much diminished. The other neurologic disturbances remained unchanged. He left the hospital against

advice, and unfortunately it has not been possible to collect any additional data.

Summary. A case of pernicious anemia with rapidly advancing combined degeneration of the cord and urinary infection, in which slight but definite improvement occurred in both subjective symptoms and in some objective signs.

CASE 2.—E. H., Unit No. 12295, a white male, aged 44 years, was admitted to the medical service of the Johns Hopkins Hospital May 25, 1927, complaining of shortness of breath; subsequently he has been readmitted frequently, the last time September 22, 1930. In the past he had enjoyed excellent health. Ten months before initial entry, the present illness began, and he noted breathlessness on exertion, associated with a general weakness. He had become pale but had never had glossitis, paraesthesias or diarrhea.

Physical examination showed a general pallor of yellowish tint, slight pitting edema of the ankles, and the palpable edge of a hard spleen at the costal border. There was no atrophy of the lingual papillae and no signs indicative of central nervous system disease.

Examination of the blood revealed R. B. C., 1,800,000 per c.mm.; Hb., 48 per cent, and W. B. C., 6400 per c.mm. In the smear there was marked anisocytosis, poikilocytosis, macrocytosis, and many nucleated red blood cells. The van den Bergh test showed an indirect reaction of 6 units. The Wassermann reaction was negative. Gastric analysis revealed 5 degrees of free hydrochloric acid after an Ewald test meal. The test, however, has been repeated many times, and even after the administration of histamin, there has never since been free hydrochloric acid in the gastric secretion. He was given adequate doses of liver and discharged much improved 5 weeks after admission with a hemoglobin of 82 per cent and R. B. C., 2,800,000 per c.mm.

Course. Three months after discharge he returned feeling as well as he ever had in his life with a blood count showing Hb., 90 per cent and R. B. C., 4,200,000 per c.mm. Six months later, 2 months after an appendectomy at another hospital, he returned feeling weak, tired out and complaining of painful swelling of the arms and legs. He was readmitted to the hospital with temperature up to 101° F., and a leukocytosis ranging between 10,000 per c.mm. and 13,000 per c.mm. The red blood count had fallen to 3,000,000 per c.mm., and the hemoglobin to 70 per cent. Over both legs there were multiple, small, red, elevated, tender areas which were characteristic of phlebitis migrans. He was given 400 gm. of liver daily, but the blood count did not rise and there was no reticulocyte response. The temperature returned to normal, and though the thromboses disappeared, the leukocyte count never became normal up to the time that he left the hospital.

He did not return for 7 months, when he gave a story of having almost entirely discontinued liver 4 months previously. He had grown worse steadily with weakness, breathlessness on exertion, progressive numbness and tingling in the hands and feet, and increasing pallor. The red blood count had fallen to 2,400,000 per c.mm. and the Hb. to 60 per cent. Vibratory sense was almost completely lost below the knees but there were no other neurologic disturbances. He was told to take 5 vials daily of Lilly's liver extract, and to supplement this with 2 or 3 pounds weekly of cooked liver. He did not return, however, for 5 months, though he followed instructions religiously. During the interval, he had had repeated sore throats, attacks of bronchitis, and he had remained weak and generally poorly. The numbness and tingling had become worse, and he had noticed that he was extremely clumsy with his hands, was unable to button buttons and that his handwriting had become almost illegible. He constantly felt as if he were walking on cotton, and when he walked in the dark he was unable to tell where his feet were, and very often was forced to seek support.

The temperature was 101° F. and the leukocyte count was 20,000 per c.mm.; R. B. C., 4,100,000 per c.mm.; Hb., 82 per cent. The tongue was very sore and red, and there was advanced atrophy of the papillæ. Though there was slight pitting edema of the ankles, there was no other evidence of phlebitis. His gait was definitely ataxic, and his station was so unsteady that when he closed his eyes he almost fell. Vibratory sense was lost on both sides below the iliac crests, there was partial loss of sense of position in the feet, and he was extremely ataxic with finer movements both in the hands and feet. Careful search was made for infection in the upper respiratory tract, the lungs, teeth, gall bladder, and genitourinary tract, but none was found. After remaining in the hospital for a short period the temperature became normal and he was discharged unimproved.

Five months later as his ataxia had increased he was readmitted to the hospital and remained on the ward for 8 months. On admission the neurologic findings were as described above. Blood examination revealed R. B. C., 4,100,000 per c.mm.; Hb., 85 per cent; W. B. C., 16,000 per c.mm. There was constantly a little fever but never over 100.5° F. Again the most careful search for some obscure hidden infection was without result. He was given enormous quantities of liver in the form of cooked liver, raw liver emulsion, Castle and Bowie's extract and Lilly's and Valentine's extracts. For months at a time he took as much as 10 pounds of liver weekly, or its equivalent in extract, and left the hospital with Hb., 81 per cent; R. B. C., 3,600,000 per c.mm.; W. B. C., 14,000 per c.mm.; and no definite change in the neurologic disturbances. Thyroid extract, and large quantities of vitamin B had been administered in addition to liver.

Summary. A patient who under treatment, which however, had been discontinued for long periods, developed signs and symptoms of combined degeneration of the spinal cord. The course of his illness was complicated by several infections. Even on enormous amounts of liver and various liver extracts, there was no improvement and perhaps some progression of the neurologic signs and symptoms with the persistence of some anemia.

CASE 3.—E. J., Unit No. 24724, an actress and acrobatic dancer, aged 29 years, was admitted to the Johns Hopkins Hospital, May 14, 1929, complaining of numbness in her legs and "weakness" of such a degree that she was unable to walk.

The patient's mother, who died in her 42d year of an "inflammation of the kidney," was considered "very anemic" during the last several years of her life. The father died at 59 years of "Bright's disease." The patient had no sisters and her only brother died at 40 years of tuberculosis.

Aside from measles, mumps, pertussis and varicella in childhood, she had had no infectious diseases and no serious illnesses until 1926. In 1918 she had had a laparotomy at which time her appendix and possibly some pelvic organs had been removed. From the age of 16 years she had followed the theatrical profession as an acrobatic dancer, and, owing to constant travelling, her dietary habits had become very poor.

Her *present illness* began about October, 1926, 2½ years before admission, when, during the course of one of her dances, she "strained" her back. Two or 3 days later she developed pneumonia and was in bed for about 3 weeks. During convalescence she noticed for the first time a numbness in her feet. At that time her blood was examined by a physician who told her that she had too few "red corpuscles" and advised her to rest and eat liver. This advice she ignored. In the latter part of November, 1926, she had regained sufficient strength to return to the stage. Although aware of numbness in her feet from time to time she felt quite well, and continued to work until the spring of 1928 when she developed "septic poisoning" supposed to have arisen from a bad tooth. After 7 weeks in bed, she recovered slowly and returned to work in the early summer of 1928. In

November, 1928, she had an attack of "pleurisy" with fever, severe pain in the right chest, and nausea and vomiting. Coincident with the "pleurisy" there was perhaps a slight increase in the numbness of her feet. In February, 1928, she developed "flu," had high fever, chills and delirium, and was in bed for 2 weeks. In March, 1929, she returned to her acrobatic dancing. About the first of April the numbness in her feet seemed to creep upward toward the knees, and for the first time she had trouble in controlling the "muscles of her legs" during her dances. Toward the middle of April her legs felt numb all over, were frankly weak, and her knees were so "wobbly" that they gave away beneath her several times. Her gait became unsteady and insecure, and at night she had severe "jumping cramps" (when observed on the ward they were found to be clonic contractions) in her thigh muscles. April 20 she found it impossible to continue with her dancing. About this same time she also noticed weakness and stiffness of her arms and hands, particularly in grasping objects. The first of May her tongue and mouth became sore. May 12 she developed numbness and tingling of the palmar surface and fingers of the left hand. When she came to the hospital May 14 her legs had become so weak and uncontrollable that she had to be supported by friends. Additional symptoms noted were: increasing constipation, requiring a purgative for almost every bowel movement, frequency of urination and loss of 20 pounds in weight in 3 months.

Physical examination. Temperature, 99° F., pulse, 68; respirations, 18; blood pressure, 120 systolic and 60 diastolic; weight, 131 pounds; height, 5 feet 3½ inches. A well-nourished woman with unusually well-developed muscles. The lingual papillæ were quite prominent. There was no stomatitis, glossitis or papillary atrophy. The heart and lungs showed nothing abnormal. The muscles though very well developed, were in general somewhat weak. In both hands the grip was diminished. Both legs were weak in all muscle groups but could be moved voluntarily in any direction. There was marked spasticity of the legs with resistance to passive motion at the knees and ankles. There was no localized muscular atrophy and no fibrillary twitchings. In the finger-nose and finger-finger tests the arms showed no ataxia or tremor. The heel-knee test showed marked clumsiness and ataxia of both legs. The patient could not stand without support, and with the eyes closed her station became very unsteady. Attempts at walking revealed a spastic, ataxic gait. Passive movement of the toes and feet was not recognized, and the patient had not the vaguest conception of their position in space. The sense of position was good in the arms and hands. She complained of severe constipation and frequency of urination but otherwise nothing to suggest sphincter disturbances.

The speech was somewhat slow but articulation was quite clear in repeating test phrases. There was no suggestion of "slurring" or "scanning" of speech.

Sensory. Numbness in the fingers and palm of the left hand; numbness of the legs was of such a degree that she felt as if they had been cut off at the hips. No demonstrable alterations in cutaneous sensibility in the arms. Sensation over the trunk normal except for a sense of pain when pressure was made upon the second and fourth lumbar vertebrae. In both legs below level of the knees a sharp diminution in appreciation of light touch and ability to distinguish sharp and dull objects. Nowhere was the loss of sensation complete. Between the knee and midthigh region the loss was less marked and above the latter level all stimuli were clearly recognized. No definite disturbance of thermal sensibility. Vibratory appreciation, though good in both arms, was totally absent below the knees. At the iliac crests vibratory sense was fairly acute. Small objects could be quite well recognized when placed in either hand.

Reflexes. The biceps, triceps and periosteoradial tendon reflexes were hyperactive in both arms. The patellar and Achilles reflexes were greatly increased. The abdominal reflexes were quite active but not abnormal. There was no patellar or ankle clonus. On both sides plantar stimulation and descending tibial irritation brought about a pronounced dorsal flexion of the great toe with fanning of the other toes.

Urine. Cloudy amber; specific gravity, 1.018; reaction, acid; sugar, negative; albumin, negative; many leukocytes, no red blood corpuscles and no casts; bile test, negative; Schlesinger's test for urobilin, +; benzidine test negative.

Blood. R. B. C., 2,390,000 per c.mm.; Hb., 60 per cent; W. B. C., 9400 per c.mm.; anisocytosis and poikilocytosis; color index, 1.25. The differential count was as follows: Polymorphonuclear neutrophils, 82 per cent; eosinophils, 0; basophils, 0; small lymphocytes, 14 per cent; large lymphocytes, 1 per cent; large mononuclears and transitionals, 3 per cent. The Price-Jones curve showed two peaks to the right of the normal with an average diameter of 8.51 micra.

The blood Wassermann reaction was negative.

The cerebrospinal fluid obtained by lumbar puncture was clear and under normal tension. It contained no cells and no globulin. Wassermann and colloidal mastic tests were negative.

Chemical examination of the blood plasma showed nonprotein nitrogen, 36 mg. per cent; uric acid, 2.7 mg. per cent; van den Bergh reaction, indirect trace.

Gastric Analysis. (1) Fasting contents: 8 cc. of fluid, free hydrochloric acid, 0 per cent; combined acid, 0.1 per cent; (2) 40 minutes after test meal of 100 cc. of 70 per cent alcohol: 9 cc. of fluid, free hydrochloric acid, 0 per cent; combined acid, 0.1 per cent; (3) 40 minutes after 1 mg. of histamin had been administered subcutaneously: 35 cc. of fluid, free hydrochloric acid, 0 per cent; combined acid, 10.5 per cent.

Course. After a control period of 5 days the patient was placed upon a diet containing 400 gm. of cooked liver daily. The response on the part of the blood is shown in the accompanying Chart I. The alleviation of symptoms, however, did not parallel the improvement in the blood picture. Emotionally she was very unstable and proved to be a difficult individual to handle. She was entirely upset by trivial incidents and wept often for hours or even a whole day without sufficient cause. At other times she was very sullen and became enraged by simple requests.

The patient's mental attitude began to improve only when she became aware of the fact that the neurologic abnormalities were disappearing. Until June 1 she believed that her legs were getting weaker and increasingly numb; in addition numbness began to be noticeable in her right hand as well as her left. Her legs at one time became so weak that she could scarcely raise them from the bed. She could not sit up without support, and she had to be helped when she wished to turn in bed.

June 1 she could, for the first time, feel the bed clothes over her feet and legs. June 8, she moved her legs. Gradual improvement continued and on June 17 she was able, for the first time, to stand erect when given a supporting hand and, although she was still unable to recognize the position of her toes, she had an indistinct but generally correct appreciation of ankle movements. Liver was increased to 600 gm. a day. June 22, with constant steadying by two attendants, she was able to take a short walk in the ward. Her gait was slow, deliberate, ataxic.

When she was discharged from the hospital July 9, she was able to stand alone by supporting herself with a chair or other object, and by holding a railing she could take 10 or 12 ataxic steps alone. Aside from the improvement in her mental condition and the increased strength of her legs, together

with a complete disappearance of the paresthesia of the upper extremities and a diminution of those of the lower extremities, the neurologic picture remained unaltered at the time of her discharge. Hyperesthesia over the legs, loss of vibratory sense, loss of sense of position of the toes, ataxia, hyperactive reflexes and bilateral positive Babinski signs were still outstanding points, and when she left for home the prognosis still seemed very doubtful.

Throughout her stay in the hospital the patient had exhibited a decided dislike for liver, and since she could not afford a commercial extract, she was instructed in the preparation of liver according to the directions of Castle and Bowie. She was told to take the equivalent of $1\frac{1}{2}$ pounds of liver each day of the Castle and Bowie extract. This she did until September 4, when, because of her remarkable improvement, and because of the

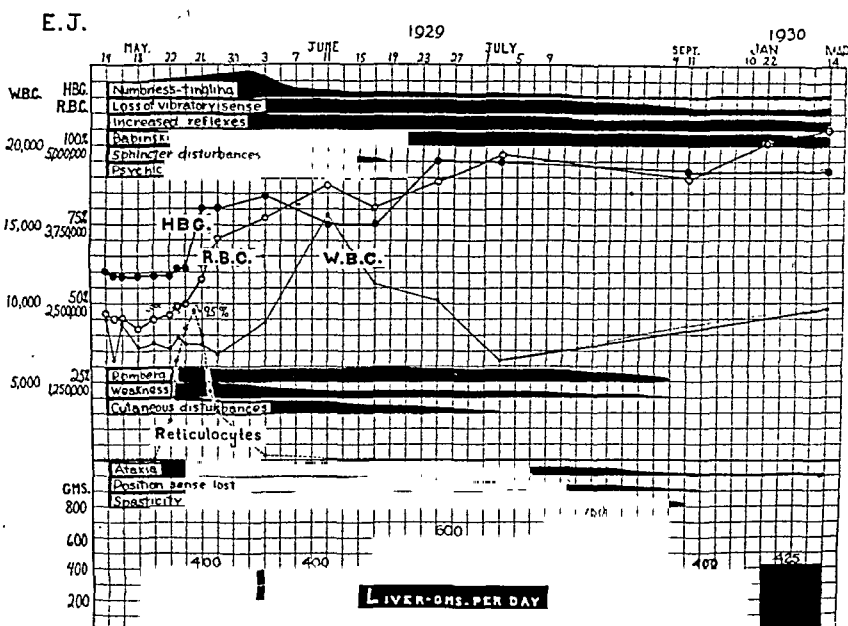


CHART I.—Case 3. Showing changes in the blood count, and in the symptoms and signs referable to disease of the nervous system during prolonged treatment by liver in a case of pernicious anemia with combined degeneration.

fact that extract prepared in anyway whatsoever actually nauseated her, it was reduced to $\frac{3}{4}$ pound a day.

Her family noticed no very great change in her condition until about August 10, when she found that the numbness had about vanished from her legs that walking was less arduous and that her sense of balance was much better. Following this each day brought a conspicuous change. By September 1 she felt that she had actually gained control of her legs again, and walked about with confidence, moving up and down stairs at will. She had several bad falls when her "knees gave way from under her" but persisted in her efforts, and by the time she returned to the hospital, September 11, she had established confidence enough to walk across streets on which there was very heavy traffic. She said that during the 3 days before her return she had felt perfectly normal, except that her legs tired and felt a

little unsteady toward evening, especially after she had been walking about much during the day.

She now walked with a rapid, vigorous gait which appeared quite normal. She stood at ease with her feet rather more widely separated than normal but there was no swaying, and she did not appear to be making any unusual effort to balance herself. Her general physical condition was excellent and mentally she was alert and happy. The neurologic status at the time was so much the same as that which will be detailed below that we shall not enter into its particulars.

She returned March 14, 1930, and as can be seen from Chart I the blood count had remained at a high level. She seemed very strong and active, and told us with pride of a four-mile walk she had taken the day before. The cranial nerves all functioned perfectly. There was no atrophy of the muscles, but on passive movement it was possible that there was slightly more tone in the right than in the left leg. The strength in all muscle groups was excellent. The finger-nose test was performed excellently as well as finer movements with the fingers and hands. In the heel-knee test there was only the slightest uncertainty, but the heel at no time left the shin. She walked with the feet deflected slightly outward and turned about cautiously. She could not walk a line accurately but there was no Romberg's sign.

She complained of only slight numbness of the feet and ankles after an active day. Touch, pain and temperature stimuli were well perceived. The sense of passive movement, two point sense and stereognosis were intact. The vibratory sense was somewhat, but not greatly, diminished below both knees. All the tendon reflexes were equal but a little more active than normally. There was no clonus. Plantar stimulation on the right gave constantly an extensor response but on the left the response was predominantly flexor.

Subsequent Course. On May 29, 1931, she was admitted to the hospital suffering from exophthalmic goiter. Five months before entry she caught a bad head cold, her eyes became "puffy" and "watered" excessively and double vision appeared. She "worried along" for a time and finally came to the Wilmer Ophthalmologic Institute, where it was found that she had marked exophthalmos and bilateral paralysis of the superior rectus muscles. As the basal metabolic rate was increased, she was admitted to the hospital. For the month before admission she had noticed increased appetite, easy excitability, and a sense of fullness in her neck and a loss of 7 pounds. There had been no symptoms indicating progress of the neurologic manifestations of the pernicious anemia.

Physical Examination. Temperature, 99° F.; pulse, 120; respirations, 24; blood pressure, 130 systolic and 70 diastolic.

She was overactive and nervous, crying frequently at the thought of an operation. The skin was bathed in a profuse perspiration and there was marked tremor of the fingers, hands and tongue. Pronounced exophthalmos was accentuated by paralysis of both superior rectus muscles, and there was lid lag, failure of convergence and diplopia. Examination of the buccal cavity, lymph nodes, heart and lungs revealed nothing remarkable. Both lobes and the isthmus of the thyroid gland were enlarged and firm. The tip of a firm spleen was felt just below the left costal margin when she drew a deep breath.

Except as noted above, the cranial nerves functioned normally. Muscle strength seemed excellent and her gait and station were unchanged. There was slight ataxia in the heel-knee test, more marked on the left than on the right. Finer movements with the fingers and hands were poorly done, probably because of the pronounced tremor. There was no spasticity. Position sense was definitely impaired in both feet, and vibratory sense was prac-

tically absent below the knees. There were no other disturbances in cutaneous sensibility.

Blood. R. B. C., 3,590,000 per c.mm.; Hb., 75 per cent; W. B. C., 7000 per c.mm.

Urine. Clear, amber, 1.018; acid; sugar, negative; albumin, negative. Sediment: Scattered leukocytes but no casts or red blood cells.

Wassermann reaction. Negative.

Basal metabolic rate: +38 and +46.

At the present time she is being prepared for subtotal thyroidectomy.

Summary. A young woman, who, about 2½ years after the appearance of numbness and tingling and immediately following a series of infections, developed rapidly progressing paraplegia with sensory disturbances in lower extremities, ataxia, hyperflexia and bilateral Babinski sign; marked improvement with return to comparatively normal life following treatment with 400 to 600 gm. of liver a day. Pronounced improvement did not occur until patient had been on treatment for 3 months. Two years after first admission there developed exophthalmic goiter.

CASE 4.—L. S., Unit No. 15874, a white woman, aged 48 years, was admitted to the Johns Hopkins Hospital, December 20, 1927, and discharged March 18, 1928. She was readmitted January 5, 1929, and discharged January 12, 1929. She complained of inability to walk. Past history and family history were not important. The present illness began about 9 weeks before entry with severe nausea, vomiting and diarrhea, lasting 2 weeks and leaving her weak. Five weeks before admission, there were pricking sensations and numbness in her hands and feet. She took to bed and remained there until admission, chiefly because she was not able to walk. Four weeks before admission, she was told she had a severe anemia. She became much worse; breathlessness on exertion set in and she frequently felt as if there were tight bands drawn about her abdomen; her feet and hands became very cold. Two weeks before admission frequent voiding, and burning on urination appeared and she had a dull, aching pain in the lower part of her back.

Physical Examination. Temperature, 99° F.; pulse, 70; respirations, 20; blood pressure, 130 systolic and 80 diastolic. Well developed, slightly obese, unable to walk. Skin was pale and slightly yellowish. The tongue very pale, showing papillary atrophy. Examination of the head, lymph nodes, neck, heart, lungs, and abdomen revealed nothing of importance.

Neurologic Examination. The cranial nerves all functioned normally. While the general musculature was well developed, the muscles were distinctly flabby on palpation. Passive movement revealed distinct rigidity in the legs, but none in the arms. The grips were distinctly weak, and there was marked weakness in both legs. There was slight ataxia in the finger-nose test, and gross ataxia in the heel-knee test, more conspicuous on the right side than the left. Finger movements were stiff and clumsy when she attempted to form finer coordinated movements. She was quite unable to walk or stand. There was slight diminution of pain perception below the wrist joints and the middle of the thighs, but the alteration was not great. Sense of passive movements of the fingers was definitely though slightly impaired, lost in the right foot, and greatly diminished in the left. Vibratory sense was lost in both legs below the knees; there was some astereognosis in both hands. The tendon reflexes were all equal, very active and abnormally increased at the knee and ankle; there was sustained ankle clonus. The plantar response was extensor on the right, though not definitely so on the left.

Blood. R. B. C., 3,660,000 per c.mm.; W. B. C., 8500 per c.mm.; Hb., 80 per cent. C. I., 1.09; differential formula: P. M. N., 62 per cent; P. M. E., 0 per cent; S. L., 37 per cent; L. M., 1 per cent. The red blood cells did not look unusually large, but there was definite anisocytosis and poikilocytosis.

Urine. Cloudy; specific gravity, 1.015; acid; sugar, negative; albumin, negative. In the sediment there were many pus cells in large clumps, and a considerable number of epithelial cells, but no red blood cells or casts.

Urine culture: Heavy growth of colon bacillus.

Wassermann reaction, negative.

Gastric analysis. Complete achlorhydria. **Blood chemistry:** van den Bergh test, indirect trace.

Course. The changes in the blood, the quantities of liver ingested, and the progress of the neurologic disturbances are shown in Chart II. Upon cystoscopic examination the bladder was found to be intensely red and swollen. Upon adequate treatment with silver nitrate instillations the infection cleared up rapidly. The blood count rose rather rapidly, and coincidently with this her general strength improved and her usual sense of

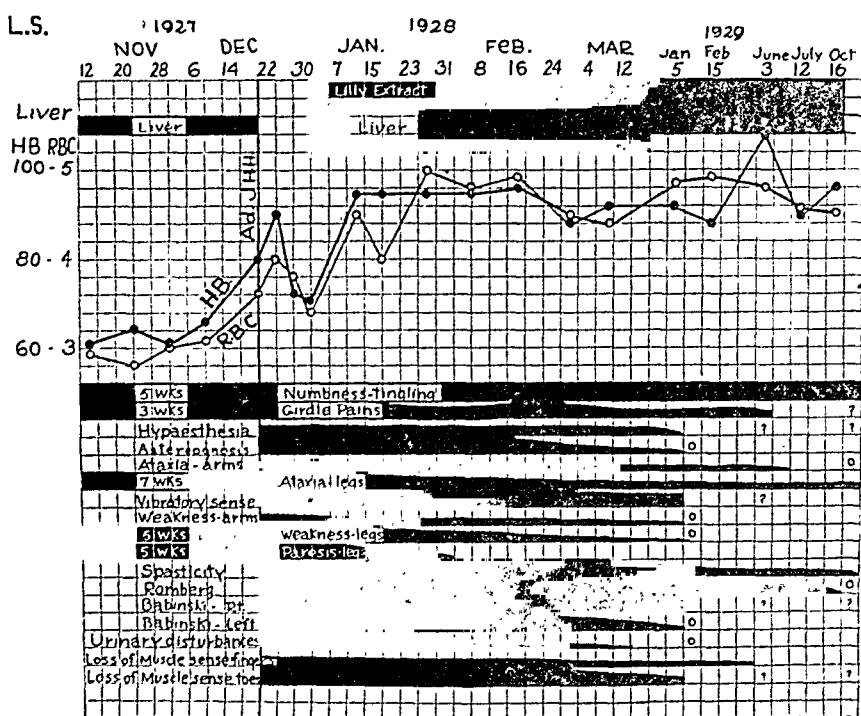


CHART II.—Case 4. Showing changes in the blood count and in the symptoms and signs referable to disease of the nervous system during prolonged treatment by liver and liver extract in a case of pernicious anemia with combined degeneration.

well-being returned. By the first of February, 1928, she was able to be up and walk for about 30 minutes with the aid of a nurse, and cane, though the gait was extremely spastic and ataxic. By the time she left the hospital, she was able to walk with a cane alone for a short distance, but the other neurologic disturbances had not shown any improvement.

Second Admission. She returned to the hospital January 5, 1929, stating that she had shown steady and remarkable improvement with a gain of 30 pounds in weight. The numbness and tingling in her extremities, though still present, had diminished to a considerable degree, and she was able to walk without assistance, if she took things slowly.

The general physical examination revealed nothing of importance. A complete neurologic examination revealed remarkable improvement in her general muscular strength, ability to walk without assistance, with only a slightly broadened base and uncertainty in turning and finally a consider-

able diminution in the paresthesias. On the other hand, the loss of sense of position and vibratory sense, the ataxia in finer movements, the extensor plantar response on the right and the exaggerated reflexes remained essentially unchanged.

Blood. Hb., 97 per cent; R. B. C., 4,650,000 per c.mm.; W. B. C., 6950. Examination of the smear revealed a normal differential formula and normal appearing red blood cells.

On January 31, 1930, the blood count was Hb., 85 per cent; R. B. C., 4,900,000: On April 21, 1931, the Hb. was 90 per cent, and R. B. C., 4,380,000. She wrote on July 9, 1931, that she walked without difficulty, bathed frequently in the ocean, weighed 156 pounds, but that she still had numbness and tingling in the hands and the feet and girdle sensations. She had taken regularly three vials daily of Lilly's liver extract.

Summary. A woman aged 48 years, suffering from pernicious anemia with rapidly progressing signs and symptoms of funicular myelitis resulting in paraplegia. There was great symptomatic improvement on treatment with liver extract so that after 10 months she was able to lead a comparatively normal life. Three years after treatment was started, numbness, tingling, and girdle sensations still persisted.

CASE 5.—W. D., Med. No. 56415, Unit No. 9151, an automobile painter, aged 49 years, was admitted to the Medical Service of the Johns Hopkins Hospital November 29, 1926, and was discharged February 8, 1927. He complained of weakness, anemia and inability to walk. No member of his family had suffered from anemia. His past life had been singularly free from illness. Mumps, measles and frequent sore throats alone disturbed his childhood. Fifteen years before entry he had suffered slightly from arthritis for 2 months. There had been no venereal infections, and he was the father of two healthy children. For 30 years he had worked with paints but had always been particularly careful to avoid "poisoning," and had never suffered with abdominal cramps or pains in the extremities.

The *present illness* began about 18 months before entry with a gradually developing weakness and general "run-down" condition. The weakness was the chief symptom for 6 months, and with it he experienced periodic "sinking spells" when he would shake all over for several minutes until he could obtain relief with ammonia. He never lost consciousness. Six months after the onset of weakness his tongue and the adjacent buccal surfaces became extremely tender and sore, and remained so for 2 months; 9 months before entry, because of the increasing weakness, he had been forced to quit work. At this time he began to notice some difficulty in walking in the dark so that he would stagger and occasionally fall. There was no vertigo. Coincident with these symptoms there were progressive sensory disturbances, including numbness and tingling in the extremities, a feeling of walking on cotton and inability to perform finer movements such as buttoning his clothes and lacing his shoes. Both gait disturbances and paresthesias progressed steadily and rapidly. The sexual reflexes completely disappeared. His appetite had decreased at first markedly but had slowly returned; in spite of which he had lost 20 pounds in the 6 months prior to entering the hospital. He had never had diarrhea or any other gastrointestinal disturbances. Many doctors had examined him and had recommended treatment for anemia which they had all said was evident. His blood had never been examined.

Physical Examination. Temperature, 100.4° F.; pulse, 104; respirations, 24; blood pressure, 118 systolic and 70 diastolic; weight, 108 pounds; height, 5 feet 3½ inches. The patient was of medium stature, and showed evidences of recent loss of weight. He looked tired and drawn and pale. The lips and mucous membranes of the mouth were pale; there was no abnormal buccal pigmentation. There was definite but not marked atrophy

of the papillæ of the tongue. A small nodule, the size of a walnut, without a thrill or bruit over it, was felt in the right lobe of the thyroid. The lungs were clear to percussion and auscultation. No enlargement of the heart was detected, and the sounds were loud and clear; no murmurs were heard. The spleen was just palpable at the left costal margin on full inspiration. The rectal sphincter seemed of good tone.

Neurologic Examination. The function of the cranial nerves was normal except for slight anisocoria, the right pupil being somewhat smaller than the left, but both reacted well to light and during accommodation.

The entire musculature was flabby and wasted with slight diminution in strength of the arms but very marked weakness of both legs. No actual paralysis. Some uncertainty without actual ataxia on finger-nose test; and finer movements, such as writing and fastening buttons, were done clumsily. The heel-knee test showed both great ataxia and weakness. When the patient stood with the eyes closed he swayed grossly, and without support would fall. He could walk only a few steps with support, and even then weakness and ataxia were marked. No speech defect. Considerable urgency in micturition.

The patient complained of numbness and tingling in the arms up to the shoulder, and in the legs up to the hips. This disturbance in sensibility caused an alteration in all cutaneous sensations so that a touch felt like an electric shock, and the tuning fork seemed to vibrate when it had not been set in motion. These sensory changes were maximal peripherally, and faded out proximally without sharp demarcation. Pin pricks were sharp everywhere, and cotton wool was well felt. Vibratory sense was lost over both legs, and the anterior superior iliac spines, but was unaltered elsewhere. There was some difficulty in recognizing small objects by touch, and sense of passive movement of the toes was completely lost. He had never complained of pain.

Tendon reflexes equal and active in the arms; knee jerks active, left sluggish. The ankle jerks were absent. The plantar reflexes were predominantly extensor in type. No clonus. The abdominal reflexes were active in the upper quadrants; absent in the lower.

There was normal response to faradic and galvanic stimulation in all muscle groups of the arms and legs.

Blood. Hemoglobin, 70 per cent; R. B. C., 3,020,000; W. B. C., 7560; color index, 1.17; P. M. N., 68 per cent; Lym., 25 per cent; P. M. E., 1 per cent; Mono., 6 per cent. In the smear the red blood cells appeared slightly larger than normal and there was moderate variation in size and shape. The platelets appeared normal and there were no evidences of regeneration noted. A Price-Jones curve showed the patient's curve to be slightly deflected to the right of the normal with the peak at 7.5 μ .

Urine. Clear; 1022; acid; sugar, 0; albumin, 0; Mic.—No casts, R. B. C. or W. B. C. Urobilin, 0.

Stool. Occult blood, 0; no parasites or ova seen.

Cerebrospinal Fluid. Clear; no blood; 5 cells per c.mm.; globulin, 0. Wassermann reaction, 0; colloidal mastic test, 0000000000.

Blood Wassermann reaction: Negative in ice-box and water-bath fixations.

Gastric Contents. Ewald test meal—free hydrochloric acid, 0; combined hydrochloric acid, 10°.

Fluoroscopic examination of the stomach revealed normal findings. In plates there was an irregularity in the pyloric region thought by the examiner to be caused by spasm.

Basal Metabolic Rate. +8.

Course in Hospital. The temperature and pulse rates became normal by the end of the first week and remained so. The changes in the blood picture symptoms and signs and the amounts of liver administered are

illustrated in Chart III. He gained 23 pounds in weight, his color improved remarkably and he felt stronger in every way. He could walk without support, but was still quite feeble and ataxic. The urgency in micturition remained. The numbness and tingling were noticed only below the knees and elbows. Vibratory and postural senses remained unimproved. There was no change in the reflexes. By February 8, 1927, as the blood picture had become practically normal, he was allowed to go home, and was urged to continue eating large quantities of liver.

Course After Leaving the Hospital. He returned for the first time in May, 1927, stating that he had improved remarkably. He no longer felt weak, and he walked with ease, driving his car and working 2 or 3 hours at a time in his garden. The sphincter disturbances had completely disappeared, and the sexual powers had fully returned. The numbness and

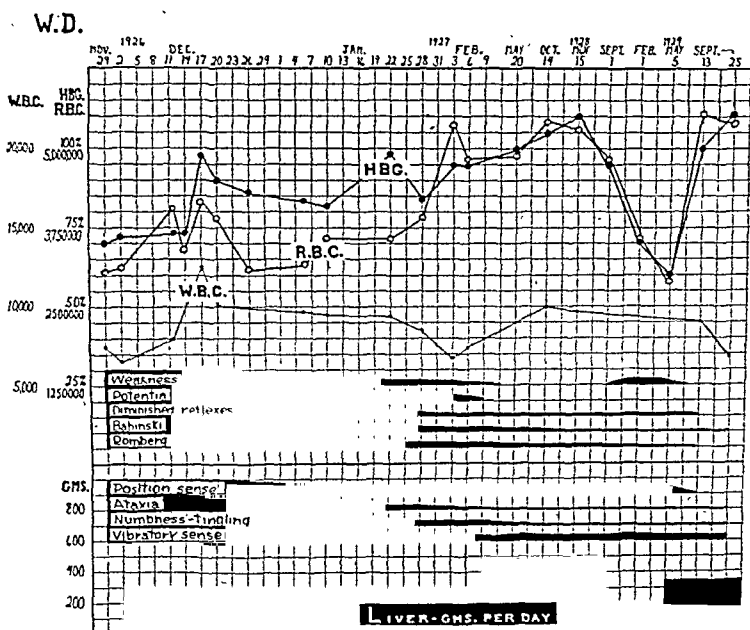


CHART III.—Case 5. Showing changes in the blood count and in the symptoms and signs referable to the nervous system during prolonged treatment by liver in a case of pernicious anemia with combined degeneration. Note the indications of relapse when the daily amount of liver is reduced.

tingling had steadily diminished and were present only in the hands and feet. He looked well and muscular, and had gained 8 more pounds. While he walked with slightly widened base, and was momentarily uncertain when he turned abruptly, there was no ataxia on finger-nose and heel-knee tests. He swayed just perceptibly when standing with the eyes closed. The knee kicks were equal and normally active but the ankle jerks could not be obtained. Plantar stimulation gave predominantly a flexor response but it was not constant. The vibratory sense was still considerably diminished below the knees, but the sense of position of the toes had returned considerably. He had taken constantly 5 pounds of cooked liver each week.

He returned periodically as is shown on the chart and though he gradually increased his activities and felt remarkably well the neurologic disturbances changed little. During the early part of 1929 he felt so well that he thought

he could diminish somewhat the quantity of liver ingested. The result of this indiscretion is shown clearly in the chart.

When seen in May, 1929, the red blood cells had fallen to 2,800,000 per c.mm., and the hemoglobin to 60 per cent. He looked quite pale, but stated that, except for a little more fatigue than usual after a long day's work, he did not notice any change in his general condition. There was no change whatever in the neurologic disturbances. He was urged to increase the intake of liver which he promised to do.

He was last seen in September, 1929, and stated that he felt as well as he ever had in his life. As can be seen from the chart the blood count had risen rapidly to a point even above normal. The muscle strength was excellent, and all tests for coördination in the arms, hands and legs were well done. The station was steady with eyes open and closed. When he walked he did not look at the ground or use a broad base, and he turned quickly, without uncertainty, but the legs were advanced in a slightly irregular fashion. Numbness and tingling were scarcely ever noticed, and then only in the tips of the fingers, the feet and ankles. There was acute appreciation of passive movement of the feet and toes. No astereognosis. There was definite diminution in vibratory sense over both legs below the knees. The tendon reflexes were all active and equal in the arms. The knee kicks were if anything a little hyperactive. The ankle jerks while a little sluggish were present and equal. Stroking the soles of the feet obliquely induced constantly plantar flexion but when the outer margins of the soles were stroked downward the response was usually extensor.

Comparing the neurologic disturbances in 1926 with those in 1929 as recorded by the same observer the following summary may be made: (1) Great improvement in muscle strength; (2) gait nearly if not quite normal; (3) station excellent; (4) almost complete disappearance of peripheral paresthesias; (5) disappearance of astereognosis; (6) return of sense of passive movement of the toes; (7) return of the ankle jerks; (8) disappearance of ataxia; (9) return of normal sphincter function; (10) return of sexual powers.

Summary. A man, aged 49 years, with slowly developing symptoms and signs of multiple degeneration of the cord, chiefly of tabetic type; fairly rapid immediate improvement on liver diet, with mild relapse after reducing the amount of liver; but return to normal health and vigor with improvement in objective signs on resumption of liver in large amounts.

Discussion. In reviewing the results of the treatment of pernicious anemia by liver, or liver extract, in this group of cases, as well as in the reported series available in the literature, one's attention is arrested by certain similarities in the effects produced upon the symptoms referable to changes in the nervous system. In the first place, the figures tend to substantiate the observation, so frequently referred to by others, that the symptoms and signs which are noticeably, and sometimes dramatically, benefited are those having to do with a disturbance of sensation or of motor paresis. Muscular weakness, numbness and tingling, even profound alterations of cutaneous or osseous sensibility, ataxia, girdle sensations and sphincter disturbances may improve remarkably or disappear entirely. On the other hand, although the Babinski sign may disappear, the exaggerated reflexes and spasticity are less likely to diminish, and though the spastic paresis may be greatly improved in some instances, such as in Case 3, this is rare. In the second place,

it seems definitely established that large quantities of liver are required to bring about the maximum therapeutic effect. In many instances the response on the part of the blood is not an accurate indication of the amounts of liver required to influence favorably the nervous symptoms. It has been frequently observed that the improvement in nervous symptoms is not commensurate with the rise in red blood cells, and that, in spite of a return of the red blood cell count to normal, the symptoms and signs, due to changes in the nervous system, persist or actually progress. One must therefore regard the nervous symptoms as being, in some way, dissociated from the blood count, and even in the presence of a normal blood count, one must increase the amounts of liver or liver extract until the ultimate possibility of affecting the nervous symptoms through this means has been exhausted. It has, moreover, been repeatedly observed that when a patient who has had only mild symptoms, such as numbness and tingling, with diminished vibratory sense, reduces the amount of liver or ceases to take liver or liver extract, the disease may relapse with only moderate reduction in the red blood corpuscles, but with rapid and alarming progression of the neurologic changes. In such cases rapid improvement may follow the ingestion of large amounts of liver. A third factor is undoubtedly one of time. Improvement in the nervous symptoms is much slower than improvement in the blood count. In many of our cases striking improvement did not take place until the patient had been on liver treatment for from 2 to 4 months. Farquharson and Graham¹⁹ lay particular stress on this point. It is of great importance, for during the entire latent period, liver should be given in large amounts and with total disregard to a high red blood cell count. And finally it must be recognized that, under liver therapy there are several accessory factors that bear directly on the rapidity and degree of improvement of practically all patients with pernicious anemia, and particularly those with subacute combined degeneration. It has been repeatedly observed that, during an infection, even large amounts of liver may fail to cause the red blood cells to rise to a high level. Patients, suffering with comparatively mild infections, such as cystitis, may not respond to liver therapy favorably, or may experience a relapse, even though they persist in taking what is presumably sufficient liver or liver extract. In the presence of an infection all the signs and symptoms of combined degeneration may persist, relapse or progress. Case 2 serves as a good example to illustrate this point. Beebe and Lewis^{22a} have recently discussed this question, and have, furthermore, drawn attention to the fact that arteriosclerosis seems to have somewhat the same effects as an infection.

With these considerations in mind it is desirable to review some of the information concerning the nature of the lesions in the nervous system, and attempt to correlate, if possible, the improvement so

frequently observed with the anatomic alterations known or supposed to exist.

Henneberg⁴ has emphasized the fact that the characteristic lesion in the spinal cord in pernicious anemia is not a sclerosis but a focal degeneration of the myelin sheaths, or of the axones, which, as the process increases, spreads upward in the posterior column and down in the pyramidal tracts. According to Henneberg, the lesion is different from that in tabes, inasmuch as the posterior roots are not involved. An increase in glia fibers, such as one sees in multiple sclerosis, does not occur. The studies of Russell, Batten and Collier,²³ as well as the more recent observations of Weil²⁴ and of Fried²⁵ lead to the same conclusion, and most authorities are now agreed that the lesion is entirely of a degenerative nature.

There is still dispute as to whether the axis cylinder or the myelin sheath is first involved. There is, furthermore, considerable evidence being accumulated to show that the lesions are, by no means, confined to the spinal cord. A few cases have been described in which anatomic lesions were found in the peripheral nerves and brain. Russell, Batten and Collier,²³ in a histologic study of the nervous system in 9 cases of subacute combined degeneration, found the peripheral nerves normal, or showing very slight change, except in one advanced case, where extensive degenerations were found in both the large trunks and the finer branches of the peripheral nerves. Mathieu,²⁶ reporting a case of pernicious anemia that showed changes both in the peripheral nerves and spinal cord, suggests that the muscular weakness and alterations in cutaneous sensibility may, in many cases, be due to peripheral neuritis. McAlpin,⁸ in discussing the matter recently, has called particular attention to certain symptoms and signs affecting the cutaneous sensations and reflexes that can be best explained as due to peripheral neuritis. Psychoses, usually manifested by depression, and ideas of persecution are not uncommon, and he points out that in some instances these symptoms may be directly connected with anatomic changes in the brain. Simons, Zador and Bielschowsky⁵ have found degenerative lesions in the peripheral nerves associated with the glossitis and papillary atrophy, and suggest that these alterations, so common in pernicious anemia, are dependent upon a peripheral nerve degeneration. Schilling²⁷ lays considerable stress upon the evidence so far adduced to show that disease of the nervous system, in pernicious anemia, is widespread, and involves not only the spinal cord but the peripheral nerves. A view, therefore, which is rapidly becoming prevalent is that, in pernicious anemia, all parts of the nervous system may be affected, including peripheral nerves, cord and brain.

There is very little information to be obtained concerning the manner, or the extent, to which these lesions in the nervous system are modified by treatment with liver or liver extract. Davison²⁸ has been enabled to study the spinal cords from 7 cases of pernicious

anemia treated by liver. The one difference which he observed between these cords and those from untreated cases of pernicious anemia was in the proliferation of glia cells. In the untreated cases this was not observed, whereas in the treated cases, instead of a poor glia response there was a definite increase in glia fibers, which is designated as a "progressive glia change."

One view which has recently been advanced to explain the origin of the changes in the nervous system in pernicious anemia is that they are dependent, as they are in beriberi, upon a vitamin deficiency. Indeed, as one studies these cases of pernicious anemia, as well as the cases of sprue, it seems more and more probable that the defect which brings about the symptoms is analogous to a vitamin deficiency. Henneberg⁴ made this suggestion sometime ago. It is conceivable that if some such deficiency existed, it might be supplied by liver or liver extract, or by meat digested with normal gastric juice or possibly by the gastric mucosa of the pig's stomach. It is known that the immediate cause of beriberi and probably of pellagra is a deficiency of vitamin B, and it has been shown further by Cogwill²⁹ and by Gildea, Kattwinkel and Castle³⁰ that lack of the anti-neuritic principle of vitamin B in the diet will result in extensive multiple degeneration of the peripheral nerves, spinal cord and brain, in dogs. These experiments have suggested that, in some way, vitamin B deficiency might be accountable for the alterations in the nervous system in pernicious anemia. In how far these suppositions may be correct it is impossible to say, but it is obvious that more extended histologic examinations of the nervous system in pernicious anemia, with particular reference to the condition of the peripheral nerves, might advance our knowledge of this important phase of the subject, and perhaps lead to a better understanding of the methods by which some of the serious nervous manifestations of the disease might be arrested or cured.

For the results obtained through liver therapy, so far, do indicate that very material benefit may be derived through this method; when it is properly employed; and, in addition, suggest very strongly that improvement proceeds in much the same way as might be expected in cases of peripheral neuritis, or possibly in tabes dorsalis. As McAlpin⁸ has pointed out, many of the nervous symptoms that are amenable to treatment by liver in pernicious anemia could be explained on the basis of changes in the peripheral nerves, and since many of these lead to a condition which renders the patient practically helpless, the restoration to a life of physical activity, which is, at times, equal to that of normal health, must be looked upon as a notable therapeutic result. Even though there still remains a group of cases in which the extent and situation of the degenerative lesions in the spinal cord excludes the possibility of repair through therapeutic procedures, it seems unreasonable on this account to neglect those cases which conceivably may be vastly improved by intensive liver therapy.

Summary. 1. The results of treatment by liver or liver extract in 44 cases of pernicious anemia, 39 of which showed signs and symptoms of definite involvement of the nervous system, are summarized.

2. The course of the disease under treatment is illustrated by an abbreviated report of 5 cases.

3. Attention is drawn to the fact that large amounts of liver must be consumed over long periods of time before great improvement becomes manifest.

4. Excluding gain in strength, improvement was noted in 31.25 per cent of the signs and symptoms of nervous system involvement in cases treated for less than 6 months, in 55.17 per cent of the signs and symptoms in cases treated for more than 6 months and in 58.93 per cent of the signs and symptoms in 8 patients with advanced subacute combined degeneration who were treated for more than 10 months.

5. The symptoms and signs that improved most noticeably were those referable to disturbances of cutaneous and muscular sensibility, and to flaccid pareses.

6. It is suggested that some of these symptoms and signs may be dependent upon changes in the peripheral nerves.

BIBLIOGRAPHY.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. Am. Med. Assn.*, 1926, 87, 470.

2. Woltman, H. W.: The Nervous Symptoms in Pernicious Anemia; an Analysis of One Hundred and Fifty Cases, *Am. J. Med. Sci.*, 1919, 157, 400.

3. Schilling, V.: Die Wirksamkeit der Lebertherapie bei der funikulären Medullose (Myelose) der Anämia perniciosa, *Fortschr. d. Therap.*, 1931, 7, 5.

4. Henneberg, R.: Atypische Formen der Funikulären Myelitis, *Klin. Wehnschr.*, 1924, 3, 970.

5. Simons, Zador, and Bielschowsky: (Quoted from Schilling).

6. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of 105 Cases, *J. Am. Med. Assn.*, 1927, 89, 759.

7. Ordway, T., and Gorham, L. W.: The Treatment of Pernicious Anemia with Liver and Liver Extract, *J. Am. Med. Assn.*, 1928, 91, 925.

8. McAlpin, D.: A Review of the Nervous and Mental Aspects of Pernicious Anemia, *Lancet*, 1929, 2, 643.

9. Starr, P.: The prevention of Spinal Cord Degeneration in Pernicious Anemia, *J. Am. Med. Assn.*, 1931, 96, 1219.

10. Seyderhelm, R.: Möglichkeiten und Grenzen der Lebertherapie, *Deutsch. Med. Wehnschr.*, 1929, 55, 1704.

11. Naegeli, O., and Gloor, H. U.: Ergebnisse einer Rundfrage über die Erfolge der Lebertherapie bei perniziöser Anämie, *Fol. Haem.*, 1930, 39, 521.

12. Smithburn, D. C., and Zerfas, L. G.: The Neural Symptoms and Signs in Pernicious Anemia: The Effect of Liver Extract, *Arch. Neurol. and Psych.*, 1931, 25, 1100.

13. Lottig, H.: Ueber Besserung der funikulären Myelitis bei Biermerscher Anämie durch Leberbehandlung, *Deutsche Ztschr. f. Nervenheilk.*, 1928, 105, 205.

14. Schilling, V.: Weitere Beobachtungen bei der Lebertherapie der Anämia perniciosa an 80 Fälle und über die Ursache von Misserfolgen und Todesfällen, *Deutsch. Med. Wehnschr.*, 1929, 55, 1701.

15. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, *Brain*, 1929, 52, 271.

16. Richardson, W.: Pernicious Anemia, *New England Med. J.*, 1929, 200, 540.

17. Davidson, S., McCrie, J. G., and Gulland, G. L.: The Treatment of Pernicious Anemia with Liver and Liver Extract, *Lancet*, 1928, 1, 847.

- 17a. Henning, N.: Weitere Erfahrungen mit der Lebertherapie bei perniziöser Anämie, *Folia Hæm.*, 1930, 42, 99.
18. Sturgis, C. C., Isaacs, R., and Riddle, M. C.: The Treatment of Pernicious Anemia by Liver Feeding, *Surg., Gynec. and Obst.*, 1930, 50, 234.
19. Farquharson, R. F., and Graham, D.: Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, *Can. Med. Assn. J.*, 1930, 23, 237.
20. Sturgis, C. C., and Isaacs, R.: Treatment of Pernicious Anemia with Desiccated Defatted Stomach, *Am. J. Med. Sci.*, 1930, 180, 597.
- Some Newer Remedies in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1930, 95, 585.
21. Conner, H. M.: The Feeding of Gastric Tissue in the Treatment of Pernicious Anemia, *J. Am. Med. Assn.*, 1931, 96, 500.
22. Baker, B. M., Bordley, J., III, and Longcope, W. T.: The Effect of Liver and Liver Extract Upon the Symptoms and Signs Referable to the Nervous System in Pernicious Anemia, *Minnesota Med.*, 1930, 13, 815.
- 22a. Beebe, R. T., and Lewis, C. E.: The Maintenance Dose of Potent Material in Pernicious Anemia, *Am. J. Med. Sci.*, 1931, 181, 796.
23. Russell, R., Batten, T. E., and Collier, J.: Subacute Combined Degeneration of the Spinal Cord, *Brain*, 1900, 23, 39.
24. Weil, A., and Davison, C.: Changes in Spinal Cord in Anemia, *Arch. Neurol. and Psych.*, 1929, 22, 966.
25. Fried, B. M.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, *J. Am. Med. Assn.*, 1929, 92, 1260.
26. Mathieu, P.: Les Syndromes Neuro-anémiques, Paris, 1925.
27. Schilling, V.: Neue Gesichtspunkte zur Umgrenzung der funikulären Myelose bei der Anämia perniciosa Biermer und über ihre Beeinflussung durch die Lebertherapie, *Verhdl. der deutsch. Gesellschft. f. inn. Med.* XLII Kong., Wiesbaden, 1930, 518.
28. Davison, C.: Spinal Cord Changes in Subacute Combined Degeneration Following Liver Therapy, *Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 639.
29. Cogwill, G. R.: Contributions to the Study of the Relation Between Vitamin B and the Nutrition of the Dog, *Am. J. Physiol.*, 1923, 66, 164.
30. Gildea, E. F., Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, *New England Med. J.*, 1930, 202, 523.

THE SIGNIFICANCE OF THE GASTRIC SECRETIONS IN PERNICIOUS ANEMIA.

BY CHARLES W. BARNETT,

INSTRUCTOR IN MEDICINE, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

(From the Department of Medicine, Stanford University School of Medicine.)

THE importance of the achylia gastrica of pernicious anemia has been suggested by Castle,^{1,2} who showed that the gastric juice of normal individuals contains a substance capable of releasing an anti-anemic substance from beefsteak. He proposes that a deficiency of secretion of this "intrinsic factor" by the stomach of the pernicious anemia patient may be the cause of the disease. If this be true, it is important to know if individuals with gastric achylia but without evidence of pernicious anemia are capable of secreting the intrinsic factor. In a brief footnote Castle³ states that he has demonstrated the intrinsic factor in the gastric juice of 3 patients of this kind. The present experiments were done in an attempt to confirm this observation.

Method. The experiment consisted in feeding to 2 patients with untreated pernicious anemia beefsteak incubated for 2 hours at 37° with hydrochloric acid, commercial pepsin and washings from the stomachs of patients with achylia but no anemia. Because of the complete achylia in the donors, the collection of sufficient pure gastric juice for the digestion was an impossibility. The maximum 10-minute secretion was less than 10 cc. The material used was obtained by washing the stomach with successive portions of normal saline and tenth-normal hydrochloric acid, alternately, for a period of about 40 minutes after the administration of histamin subcutaneously. The volume of the washings was about 300 cc. The washings were then mixed with 200 gm. of finely ground beef muscle, and were incubated for 2 hours at 37° after the addition of 2 to 5 gm. of commercial pepsin and after being brought to a pH of about 3 with concentrated hydrochloric acid. At the end of the incubation period the mixture was strained and the filtrate titrated to a pH of 5. It was then introduced by tube into the fasting stomach of the recipient.

Experimental Observations. Two experiments were carried out using 2 pernicious anemia patients as recipients and 2 achylia cases as donors.

Gastric juice for the first experiment was obtained from a patient with arteriosclerosis and hypertension, aged 64 years, who is known to have had achlorhydria to the Ewald meal since April 1, 1925, and to histamin since December 31, 1927. He presents no evidence of pernicious anemia. His blood at the time of the experiment showed the following: Red blood cells, 4,120,000; hemoglobin, 79 per cent Sahli; color index, 0.95; white blood cells, 9650; polymorphonuclears, 55 per cent; lymphocytes, 32 per cent; large mononuclears, 9 per cent; eosinophils, 3 per cent; basophils, 1 per cent; platelets, 151,000; reticulocytes, 0.2 per cent. Smear showed slight anisocytosis and an occasional small poikilocyte. The Price-Jones curve had its peak at 8 micra instead of the normal 7.5. Icterus index was 4.8. Indirect van den Bergh, 0.2 units.

The clinical record of the case used for testing the potency of the digested material is briefly as follows:

Case Report.—Mr. M. B., aged 38 years, American Store manager, entered the hospital on March 17, 1931, complaining of weakness and dyspnea on exertion for 2 months. His family and past histories were unimportant. Seven months before entry he developed anorexia, a bad taste in his mouth and slight constipation. Five months later he began to have palpitation, dyspnea on exertion and increasing weakness. His mouth was sore for a few days at about the time these symptoms appeared. Two weeks before admission his ankles became slightly swollen. At times his hands and feet were numb.

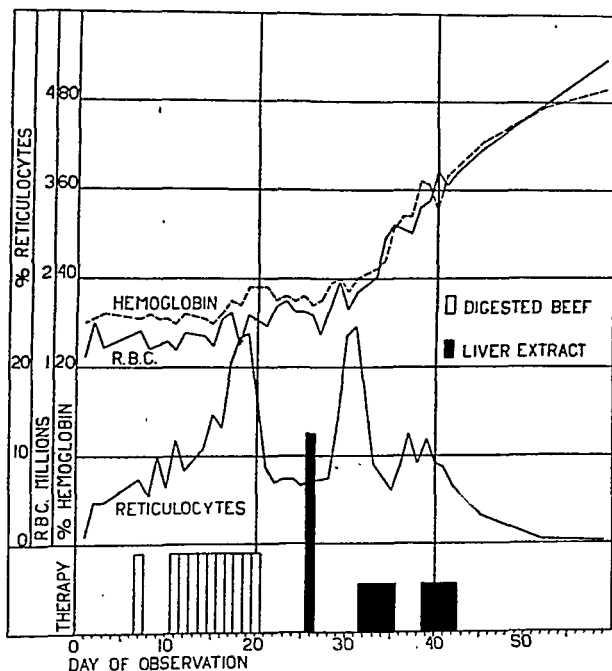
On examination, he was well nourished but pale with a distinct café au lait color. The right pupil was slightly larger than the left but both reacted. There were two patches of white exudate in the right fundus on the temporal side of the disk. The tongue was smooth but there was not a complete

papillary atrophy. The lungs were clear and the heart was normal. Blood pressure was 130 systolic and 75 diastolic. The spleen was not felt. The reflexes were normal and vibratory and joint sensibility was unimpaired. The blood count was: Red blood cells, 1,500,000; hemoglobin, 31 per cent Sahli; color index, 1.03; reticulocytes, 4.8 per cent; white blood cells, 4100; polymorphonuclears, 54 per cent; lymphocytes, 41 per cent; platelets, 45,000.

Urine, stool and blood Wassermann were negative. Gastric analysis after histamin showed a complete absence of free hydrochloric acid and the highest 10-minute volume was 4 cc.

His response to treatment is shown in Chart I.

CHART I.—RESPONSE OF CASE OF PERNICIOUS ANEMIA TO TREATMENT WITH BEEF DIGESTED IN HYDROCHLORIC ACID, COMMERCIAL PEPSIN AND GASTRIC JUICE FROM A CASE OF ANACIDITY.



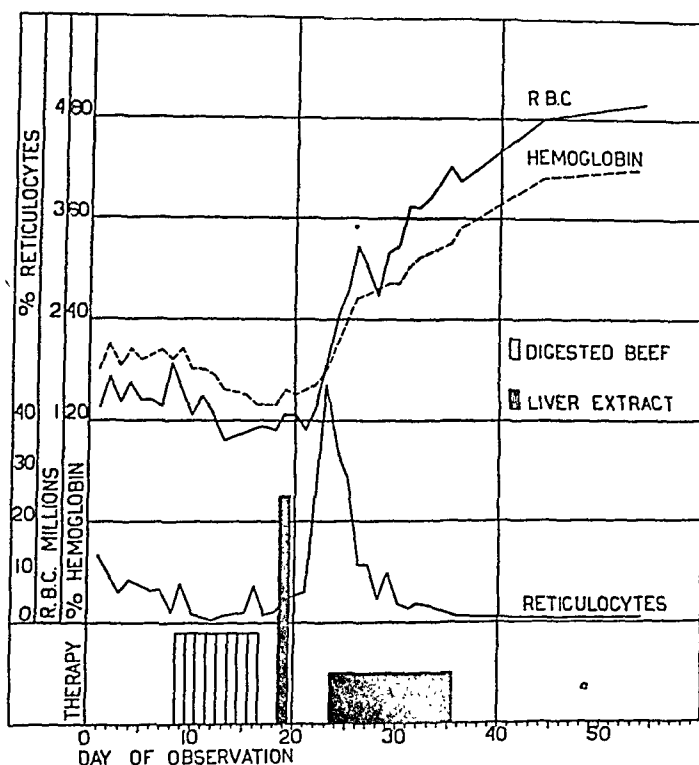
On the seventh day he was given 200 gm. of beefsteak digested as described above. On the next 3 days he received no treatment because of nausea, but from the eleventh to the twentieth days he received daily doses of the same mixture. Before the treatment was started, his reticulocytes rose to 10 per cent and during the course of treatment, to 23 per cent. There was, however, no significant rise in his red cells or hemoglobin following this reticulocyte response. On the twenty-sixth day he was given 24 vials of liver extract (Lilly 343) and later 6 vials daily. Following this he had a second reticulocyte response of the same magnitude as the first followed by a prompt rise in red cells and hemoglobin to approximately normal by the sixtieth day.

Juice for the second experiment was obtained from a patient with angina pectoris, aged 65 years, who has had an anacidity to histamin since September 17, 1929. He presents no evidence of pernicious anemia. His blood at the time of the experiment showed:

Red blood cells, 4,330,000; hemoglobin, 87 per cent Sahli; color index, 1.01; white blood cells, 6925; polymorphonuclears, 54 per cent; lymphocytes, 28 per cent; large mononuclears, 7 per cent; eosinophils, 10 per cent; basophils, 1 per cent; platelets, 337,000. The smear shows slight anisocytosis and a few small poikilocytes. The Price-Jones curve had a slightly flattened peak at 7.5 micra. Icterus index was 9. Indirect van den Bergh, 0.75 units.

The findings in the test case were as follows:

CHART II.—RESPONSE OF CASE OF PERNICIOUS ANEMIA TO TREATMENT WITH BEEF DIGESTED IN HYDROCHLORIC ACID, COMMERCIAL PEPSIN AND GASTRIC JUICE FROM A CASE OF ANACIDITY.



Mrs. F. N., a Canadian housewife, aged 48 years, entered the hospital on March 30, 1931, complaining of pain in the abdomen and back for 6 months. The family history was unimportant. The past history was negative except that she has always bruised and bled easily. Six months ago she became pale, began to lose weight and to feel weak and tired. She developed palpitation, dyspnea and swelling of her legs and hands. Five months ago she began to have dull pain in her lower abdomen and back. Six weeks ago she developed numbness and tingling in her hands and pain in her legs. All her symptoms have become progressively more severe.

She was extremely pale and showed evidence of considerable weight loss but did not otherwise appear ill. There was a marked papillary atrophy of the tongue. The lungs were clear and the heart was negative except for a soft systolic murmur. Blood pressure was 115 systolic, 60 diastolic. A firm liver edge extended 6 cm., and the spleen was palpable about 4 cm., below the costal margin. The knee and ankles jerks were not obtained and there was definite diminution of vibratory and joint sensibility in both legs. The Romberg was positive. The blood showed: Red blood cells,

1,120,000; hemoglobin, 30 per cent Sahli; color index, 1.3; white blood cells, 3100; polymorphonuclears, 37 per cent; lymphocytes, 55 per cent; platelets, 85,000; reticulocytes, 13.2 per cent; coagulation and bleeding time were normal. The smear showed marked anisocytosis, moderate poikilocytosis, polychromasia, normoblasts and a few megaloblasts. The urine and Wassermann were negative. The stool showed occult blood. Icterus index was 15; the indirect van den Bergh, 2 units.

Because of the high initial level of the reticulocytes no therapy was given until the count had dropped to about 5 per cent. She was then given a series of 8 daily feedings of the digestion mixture described above, beginning on the ninth day of observation. No reticulocyte response followed this treatment and the red cells and hemoglobin fell steadily. Because of the severity of her anemia, it was considered unwise to withhold liver and on the 19th day she was given 24 vials of liver extract, followed on the 24th day by daily doses of 6 vials. Following this treatment, there was a prompt and typical response. Her course is shown in Chart II.

Discussion. As pointed out above, the object of these experiments was to determine whether patients with complete long-standing achylia gastrica but without evidence of pernicious anemia put out the intrinsic antianemic factor of Castle in such gastric secretions as are present. If Castle's theory is correct, namely, that the absence of this factor in pernicious anemia patients is often responsible for the development of the disease, one might expect people without pernicious anemia even though they had a deficient gastric secretion in the ordinary sense still to possess the antianemic factor. Our experiments failed to show that such is the case. In the first experiment there was, to be sure, a reticulocyte response of over 20 per cent following treatment with digested beef. The response had, however, started before therapy was begun, and was not followed by any improvement in the blood: While this response does not rule out the possibility of the presence of a slight amount of the effective substance in the digestion mixture, it does not prove that it was present. In the second experiment no response whatever followed treatment with digested beef. A longer interval between this therapy and treatment with liver extract would have been desirable, but the complete absence of a response for 12 days after treatment was started pretty well demonstrates the absence of effective material. These results suggest that the absence in the gastric secretion of the intrinsic factor does not invariably lead to the development of pernicious anemia.

Summary. 1. Beefsteak digested with hydrochloric acid, pepsin and gastric juice from cases of long-standing anacidity without anemia was used in the treatment of cases of pernicious anemia. Two such experiments are described.

2. No definite response followed the treatment in either case.

BIBLIOGRAPHY.

1. Castle, W. B.: *AM. J. MED. SCI.*, 1929, 178, 748.
2. Castle, W. B., and Townsend, W. C.: *AM. J. MED. SCI.*, 1929, 178, 764.
3. Castle, W. B., Townsend, W. C., and Heath, C. W.: *AM. J. MED. SCI.*, 1930, 180, 305.

ANEMIA OF THE MICROCYTIC TYPE IN MIDDLE-AGED WOMEN.*

BY DOUGLAS VANDERHOOF, M.D.,

EMERITUS PROFESSOR OF MEDICINE, MEDICAL COLLEGE OF VIRGINIA.

AND

DEWEY DAVIS, M.D.,

ASSOCIATE IN MEDICINE, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VA.

(From the Medical College of Virginia.)

THIS report deals with 5 patients presenting a type of anemia and certain clinical features that suggest a disease entity. These patients were all women, the youngest, aged 37 years, and the oldest 46 years. A similar picture in a male has not come under observation.

The anemia in these women was essentially chronic, having lasted from 11 to 15 years in 4 cases, and at least 2 years in 1 case. There had been no remissions and there were no symptoms or signs suggesting degenerative changes in the spinal cord. Four of these women showed the typical tongue of atrophic glossitis. Gastric analysis by the fractional method showed achlorhydria in 4 cases, with no response after the hypodermic injection of 0.5 mg. histamin in 3, while 1 patient showed a slight secretion of free hydrochloric acid after the histamin. In the fifth patient achlorhydria was strongly suspected but she refused to have a gastric analysis made. All suffered from weakness, palpitation and breathlessness; 4 complained of digestive disturbances, and 3 listed diarrhea of the morning type as a prominent symptom. These 5 women all had menstrual irregularities with the history of excessive bleeding at the menstrual period. (Table 1.)

TABLE 1.—FIVE CASES OF MICROCYTIC ANEMIA—ALL FEMALES.

Name	F	C	M	H	D
Age	40	37	46	40	38
Duration, years	2	14	11	12	15
Remissions	0	0	0	0	0
Atrophic tongue	+	+	0	+	+
Achlorhydria	+	+	?	+	+
Menstrual flow	+	+	++	++	+

When these women first came under observation, the hemoglobin ranged from 40 to 58 per cent in 4, with red cell counts from 3,200,000 to 3,900,000. In the fifth patient, the hemoglobin was 65 per cent and red count 4,200,000. All showed a low color index. The striking feature of the blood picture, however, was the small size of the

* Read before the Forty-sixth Annual Meeting of the Association of American Physicians, May 6, 1931.

red blood cells. The mean diameter of the red cells was under 7 microns in every case, ranging from 6.32 microns as a minimum to 6.96 as a maximum. (Table 2.) This blood picture indicates an anemia of the microcytic type.* It may also be spoken of as hypochromic or chlorotic in character, but the total red cell count tends to be lower than in true chlorosis, and the atrophic glossitis and gastric anacidity are distinguishing features in the cases here presented.

TABLE 2.

Name	F	C	M	H	D
Hemoglobin	58	42	40	65	40
Red blood cells	3.2	3.9	3.3	4.2	3.2
Diameter red cells	6.32	6.89	6.92	6.96	6.62
After treatment:					
Hemoglobin	70	86	85	90	75
Red blood cells	4.9	4.6	5.0	4.6	4.5
Diameter red cells	7.11	7.19	7.35	7.39	

The underlying cause of this particular type of anemia is not obvious although three factors stand out in this small group of patients: they all were middle-aged women who had excessive menstrual bleeding, and gastric anacidity was demonstrated in all but 1 patient who refused the test. That the periodic loss of blood was not in itself responsible would seem to be indicated by the fact that red blood cell measurements in other females with anemia secondary to uterine bleeding have not shown microcytosis approaching the degree seen in these cases. On the other hand, if the achlorhydria were responsible one would expect to find similar blood pictures in males with achylia gastrica but this we have been unable to do. In reviewing our cases of achlorhydria we have separated the group that was uncomplicated by other diseases, such as carcinoma, pernicious anemia, chronic cholecystitis, gross sepsis, profuse bleeding and other obvious conditions. We have further divided these cases into two groups according to age. Below the age of 50 years, we find 240 instances of uncomplicated gastric anacidity made up of 69 males and 171 females. Only 3 of the males had hemoglobin readings below 80 per cent while 99 females had a hemoglobin percentage below 80.

Two reports have recently appeared on the subject of simple, or hypochromic, anemia associated with achlorhydria by Witts³ and by Waugh,⁴ with reference to previous reports by Faber, 1913, Faber and Gram, 1924, Charles Hunter, 1923, Kaznelson, 1926 and others. Witts states that the anemia in his 50 cases was of the microcytic type and 49 of these patients were women. All the cases reported by Waugh, 10 in number, were women, for the most part

* Measurement of the red blood cells by one of us (D. D.) in a series of normal individuals has shown the mean diameter to vary from 7.25 microns to 7.50 microns. Medearis and Minot¹ have reported normal variations from 7.25 to 7.75 microns, while the figures of Bell, Thomas and Means² are from 7.4 to 8 microns.

between the ages of 35 and 45 years with no case seen after the menopause. In addition to the hypochromic type of anemia with low color index, the blood shows a slight leukopenia, the platelets are normal or somewhat reduced in number, fragility tests are normal as is also the bleeding time, the van den Bergh test is negative and the reticulocytes are not increased. Witts describes simple achlorhydric anemia as a disease of middle-aged women, with its highest incidence between the ages of 40 and 50 years. He saw no case under the age of 22 years and differentiates this anemia very sharply from true chlorosis, which he defines as a secondary type of anemia occurring spontaneously in adolescent females and generally associated with gastric hyperacidity. He furthermore states that the chlorotic girl does not relapse in adult life. In this microcytic type of anemia the bone marrow is apparently able to maintain fairly well the number of red blood cells but there is an evident dysfunction in the synthesis of hemoglobin.

In individuals with the megalocytic, hyperchromic type of blood picture which we call pernicious anemia, it is well established that achlorhydria is an almost constant finding. Yet it is evident that one or more other factors must be involved, as the majority of persons with true achylia gastrica, even if untreated, do not develop pernicious anemia. In the microcytic, hypochromic anemia now under discussion, also associated with achlorhydria, some other unknown factor is evidently in operation. Limited to women between the age of full maturity and the climacteric, as this type of anemia appears to be, may not the periodic blood loss at the menstrual time, often excessive in amount, have its influence on the bone marrow? In other words, achlorhydria plus some unknown factor may result in pernicious anemia, while achlorhydria plus periodic hemorrhages may induce a microcytic type of anemia.

This type of anemia, as illustrated in our cases and as emphasized by other writers on the subject, is essentially chronic, rarely fatal, and is responsible for persistent ill health in older women. As regards treatment, Witts and others believe that the anemia can be controlled by the regular administration of large doses of iron, supplemented, if necessary, by one or more blood transfusions. Our experience with large doses of iron, in the form of Bland's mass, has been quite satisfactory, although the anemia gradually recurs after the medication is discontinued and we have found that repeated courses of iron are quite necessary. In the presence of achlorhydria, we also insist on the regular administration of dilute hydrochloric acid, 1 teaspoonful, well diluted, with meals. Witts has shown that hydrochloric acid without iron, however, has no effect on the anemia. We found this to be true in the early treatment of the first case in our series. In regard to liver feeding, some writers take the position that liver is without value in the microcytic type of anemia. Others believe that in most secondary

anemias, treatment by adequate liver feeding has been effective, whereas the use of most liver extracts has failed. We have found, however, that the aqueous liver extract, E. 29, apparently possesses the properties of whole liver and in the microcytic type of anemia under discussion brings about a very satisfactory increase in both the hemoglobin and erythrocytes, and a slight but definite reticulocyte response. (Tables 3 and 4.) One ounce (30 cc.) of this aqueous liver extract, E. 29, is equivalent to $\frac{1}{2}$ pound of whole liver and contains from 5 to 8 mg. of iron which, in itself, is not sufficient to account for its favorable effect when compared with the alcoholic liver extracts. We have found as the blood count improves that the red cells become larger and tend to approach the average normal diameter (Table 2).

TABLE 3.—MRS. M. (19672).

Date.	Hb., per cent.	R.B.C. Mil.	Diameter of R.B.C., microns.	Liver extract daily, cc.	Iron daily, gr.
August 18, 1930	40	3.3	6.92	90	30
September 3, 1930	53	4.5	90	30
September 8, 1930	62	4.5	60	30
October 20, 1930	80	4.4	7.35	60	30
December 18, 1930	85	5.1	7.26	..	30
December 20, 1930	Given 1000 mg. hours intrauterine radium.				
May 25, 1931	Patient writes recent blood count normal.				

TABLE 4.—MRS. C. (18335).

Date.	Hb., per cent.	R.B.C., Mil.	Diameter R.B.C., microns.	Reticulo- cytes, per cent.	Liver extract daily, cc.	Iron daily, gr.
October 30, 1928	42	3.9	6.89	0.6	90	0
November 5, 1928	48	4.3	2.4	90	0
November 8, 1928	52	4.3	7.19	4.4	90	0
November 13, 1928	52	4.4	2.0	90	0
December 7, 1928	74	4.7	90	0
February 9, 1929	86	30	0
March 20, 1929	75	4.1	0	0
June 8, 1929	70	4.5	30	0
March 28, 1930	60	4.0	7.19	...	90	0
March 30, 1931	65	4.2	7.16	...	0	60
June 4, 1931	80	4.7	0	60

NOTE.—March 28, 1930, patient was ordered 90 cc. liver extract daily, but took it for only a few weeks.

Finally, in the treatment of these women with microcytic anemia and excessive menstrual bleeding, one must consider the advisability of putting a stop to the periodic blood loss either by hysterectomy or by the proper use of radium or deep Roentgen ray therapy. One of our patients was given 1000 mg. hours of intrauterine radium, and a second patient has had hysterectomy for a fibroid uterus, but these procedures were done too recently to evaluate the results in this report.

Summary. This report deals with 5 patients, all women, aged from 37 to 46 years, with a microcytic type of anemia, atrophic glossitis, achlorhydria and increased blood loss at the menstrual periods.

The symptoms, clinical features and blood picture suggest a disease entity, which is responsible for persistent ill health and is often unrecognized.

Treatment consists of large doses of iron and adequate hydrochloric acid therapy. Instead of the iron, an aqueous liver extract may be used with good results. The anemia gradually recurs when treatment is omitted so that it must be resumed from time to time as determined by the blood count. Hysterectomy may be advisable to put a stop to the periodic blood loss, or this effect may be secured by radium or deep Roentgen ray therapy when indicated.

REFERENCES.

1. Medearis, D. N., and Minot, G. R.: Studies on Red Blood Cell Diameter, *J. Clin. Invest.*, 1927, 3, 541.
2. Bell, J. R., Thomas, F. K., and Means, J. H.: Studies on Red Blood Cell Diameter, *J. Clin. Invest.*, 1926, 3, 229.
3. Witts, L. J.: Simple Achlorhydric Anemia, *Guy's Hosp. Rep.*, 1930, 80, 253.
4. Waugh, T. R.: Hypochromic Anemia with Achlorhydria, *Arch. Int. Med.*, 1931, 47, 71.

AURICULAR FLUTTER: SOME OF ITS CLINICAL MANIFESTATIONS AND ITS TREATMENT.

BASED ON A STUDY OF 65 CASES.

BY THOMAS M. MCMILLAN, M.D.,

AND

SAMUEL BELLET, M.D.,

PHILADELPHIA, PA.

(From the Division of Cardiology of the Philadelphia General Hospital and the Robinette Foundation for the Study of Cardiovascular Diseases of the University of Pennsylvania, Philadelphia, Pa.)

In spite of the infrequency of auricular flutter, it, nevertheless, is a disturbance of considerable importance because of its occurrence mainly in hearts that are seriously diseased and because it is susceptible of successful treatment in a considerable percentage of cases.

There have not been many reports of flutter based on large series of cases. Among the most important are those of Ritchie, 1914,³⁵ which included 52 cases, and of Blackford and Willius, 1916,² based on 16 cases. Since the introduction of quinidin, the only published clinical report of this condition which considered a large number of cases is that of Parkinson and Bedford,³¹ a study of 52 cases.

Since 1921, we have encountered 80 instances of this disturbance. Our observations on some of these included but one electrocardiographic study; others refused hospital treatment. For such

reasons, we are basing this paper on 65 of the 80 cases. We have not attempted to consider all phases of the subject but only those portions to which the material of our series seemed to contribute something of interest.

Clinical Variations of Flutter. Auricular flutter is found either as an established disturbance or as a paroxysmal or transient condition. Any line of demarcation between these varieties must necessarily be an arbitrary one. We have accepted Parkinson and Bedford's³¹ selection of 2 weeks as the necessary duration for established flutter. It is to be borne in mind, however, that a duration of 2 weeks or even longer does not necessarily mean that flutter is permanent and may not revert to normal rhythm spontaneously: 2 of our cases returned to sinus rhythm without treatment after having fluttered continuously for 4 and 6 weeks respectively.

It has not proven an easy matter to establish the duration of all of the cases of our series. They nearly all entered the hospital with flutter: the beginning of the disturbance had to be determined from the history and the behavior of the case under observation. In Table 1, we have set down the known duration of flutter in our 65 cases after hospital admission. After considering all of the facts available to us, we divided 55 of our 65 cases into 12 of the paroxysmal and 43 of the established forms of flutter. Of the 10 unclassified cases, 7 were due either to quinidin or digitalis, and 3 were untreated. The percentages of paroxysmal and established flutter in our series (22 paroxysmal, and 78 established) were practically the same as in Parkinson and Bedford's³¹ series (25 and 75 respectively).

TABLE 1.—KNOWN DURATION AFTER ADMISSION TO HOSPITAL.

	Cases.
Less than 1 week	25
1 to 2 weeks	15
2 to 4 weeks	12
1 to 2 months	7
2 to 3 months	6

Incidence. In 1200 cases, Wedd⁴⁶ found flutter in 9 and fibrillation in 137, *i.e.*, flutter occurred once in every 133 patients and fibrillation once in every 9. Blackford and Willius² encountered flutter once in every 217 cases and fibrillation once in every 10 cases in a series of 3500 patients. Willius⁴⁸ later analyzed 40,000 cases and found flutter in 168 or once in every 238 cases. There is thus a fair similarity of both the incidence of auricular flutter and the ratio of flutter to fibrillation as determined in these large numbers of patients.

In our own experience we have found auricular flutter to be more common. In 16,000 electrocardiograms on 6500 different patients who either had or were suspected of having cardiac disease we encountered flutter in 80 and fibrillation in 464, the ratios being respectively 1 in every 80 and 1 in every 14 such patients.

Age. Our youngest patient was 12 years of age, our oldest 86, the average age being 54 years.

TABLE 2.—AGE DISTRIBUTION.

Age.	No. of cases.
10 to 19	1
20 to 29	2
30 to 39	7
40 to 49	13
50 to 59	14
60 to 69	19
70 to 79	6
80 to 89	3

Table 2 shows that the incidence of flutter was greatest over the age of 40 years, 72 per cent of our cases being between 40 and 70 when flutter first came under observation. These figures are quite in accord with similar figures in the reports to which we have referred.

Etiologic Factors. Associated Conditions. Auricular flutter is usually the result of antecedent damage of the auricular muscle, mainly due either to inflammatory or degenerative processes. At times more acute causes are operative. Among these are acute rheumatic fever,^{4, 30, 33, 44} diphtheria,¹⁸ hyperthyroidism,^{7, 20, 21, 31} and coronary occlusion.^{1, 10, 14, 42, 47}

In our series old rheumatic heart disease was present in 16 cases, hypertension in 12, syphilis in 13, thyrotoxicosis in 2, "toxic myocarditis" (pulmonary abscess and pulmonary tuberculosis) in 1. Arteriosclerosis, observed in 40 of our patients, rather than some other assigned cause, may well have been the real precipitating factor in many of them. In 2 instances, flutter was apparently caused by toxic doses of digitalis, while in 5, the disturbance was the result of the quinidin treatment of auricular fibrillation.

Auricular flutter has been reported as occurring occasionally in normal hearts.^{31, 35} In all but 1 of our cases the heart damage was severe and far advanced. In this 1 case cardiac damage was present, but of relatively slight degree.

Auricular Flutter Produced by Digitalis. The development of auricular fibrillation following the administration of digitalis has been reported to occur occasionally.^{26, 6, 8, 13, 34} So far as we are aware, Wedd⁴⁶ is the only author who has reported flutter as a probable result of digitalis. His 1 patient received a total of 25 cc. of the tincture of digitalis and 1 mg. of strophanthin intravenously prior to the onset of flutter. The disturbance was transient, lasting for 1 day only.

In our series we encountered 2 cases in which flutter followed large quantities of digitalis. A brief history of these patients follows:

Case Reports. CASE 36.—E. W. T., a colored man, aged 62 years, had had symptoms of gradually progressing congestive heart failure for 3 years.

Examination showed cardiac enlargement without valve lesions, hypertension (170 systolic and 100 diastolic), generalized arteriosclerosis and evidence of congestive heart failure. No evidence of syphilis or rheumatic fever was discovered.

After a relatively normal electrocardiogram had been obtained, the administration of 1 dram of the tincture of digitalis 3 times a day was begun. No symptoms of digitalis poisoning were noted except weakness, which by the 7th day was marked. Also on this day a nodal rhythm appeared (Fig. 1, *B*). The order to stop digitalis was unfortunately overlooked, and 2 additional doses were administered; on the 8th day, auricular flutter was present (Fig. 1, *C*). On the next day, 24 hours after the last dose of digitalis, flutter was still present and the *A-V* block had increased from 4 to 1 to 8 to 1 and even 12 to 1 (Fig. 1, *D*). The flutter persisted and death ensued the following day. The effects of atropin on the auricular and ventricular mechanism are discussed in another section of this paper.

CASE 35.—Our second case of flutter which followed large amounts of digitalis is being reported elsewhere in a paper on ventricular tachycardia, which also developed. The patient, a man, aged 65 years, with arteriosclerotic heart disease and congestive failure, received $13\frac{1}{2}$ drams of the tincture of digitalis within 10 days, or an average of $1\frac{1}{4}$ drams per day. On the 9th day of the drug's administration, auricular flutter with 3 to 1 block developed. On the following day, ventricular tachycardia set in, and death soon followed.

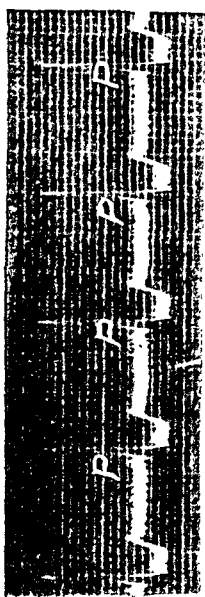
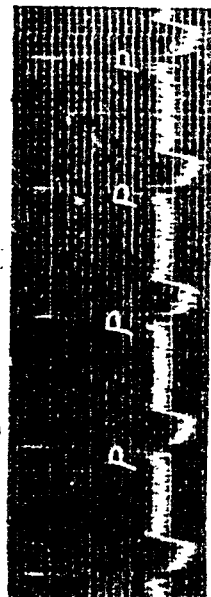
Mechanism. The exact physiologic reactions of the auricular muscle to digitalis which lead to fibrillation or flutter are not known. It is presumed that either the indirect vagal effect of digitalis or its direct action on the auricular muscle is a responsible factor. Resnick³⁴ feels that both may play a rôle in bringing on fibrillation, but that a diseased heart in addition to digitalis is probably necessary for the establishment of a circus rhythm under this drug.

In all the reported cases of fibrillation or flutter resulting from digitalis, the heart has been seriously diseased. This was the fact in both our cases, as shown by postmortem as well as by clinical study.

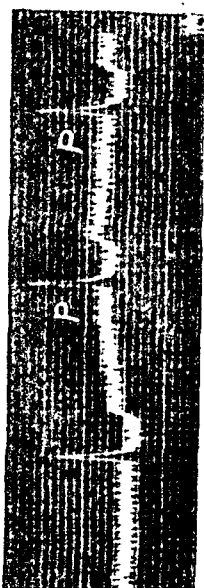
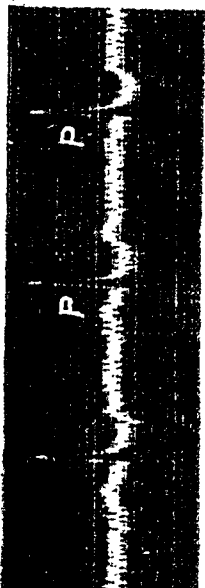
We possess no data that throw definite light on the mode of action of digitalis in inducing flutter in either of the 2 cases we are reporting. After flutter had commenced, digitalis did definitely influence the mechanism, through what we interpret elsewhere in this paper (The Auricular Rate in Its Reaction to Drugs) as vagal influences. Granting that our conclusion is correct, it does not necessarily follow that vagal action caused the onset of flutter.

FIG. 1.—Flutter following large amounts of digitalis. *A*, the three customary leads taken after 18 drams of the tincture of digitalis had been administered; *B*, the tracing obtained the following day of the administration of a total of 21 drams of the tincture of digitalis. This is interpreted as showing *A-V* rhythm; *C* (Lead II only), a tracing obtained after a total of 24 drams of the drug had been used. It shows auricular flutter with 6 to 1 block; *D* (Lead II only), a tracing taken 24 hours after the last dose of digitalis. The block is of a higher grade and coupled ventricular extrasystoles.

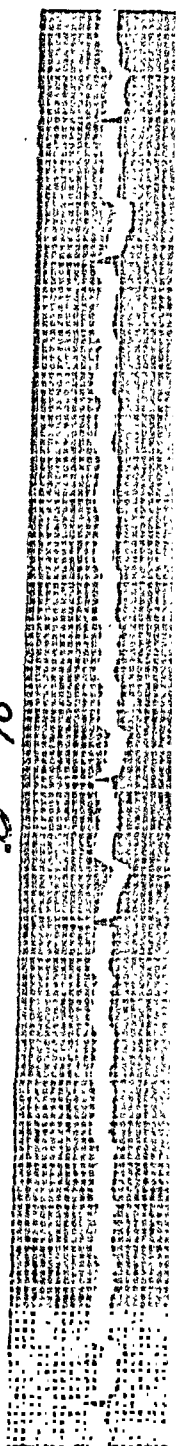
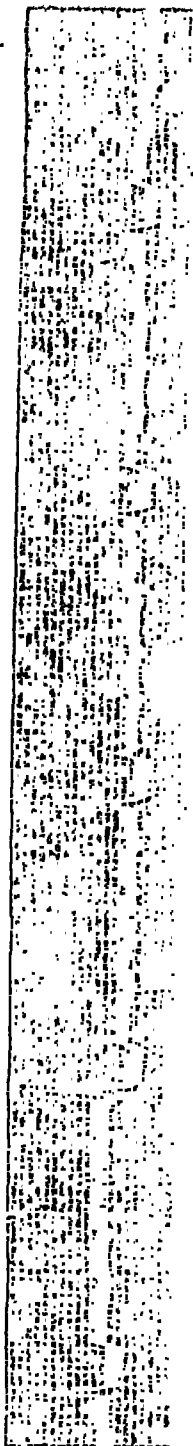
B-7/4



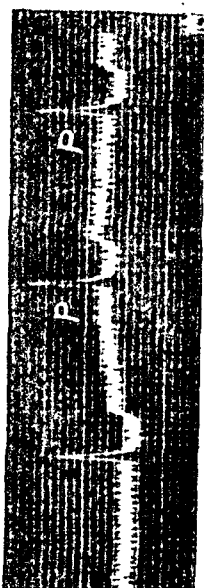
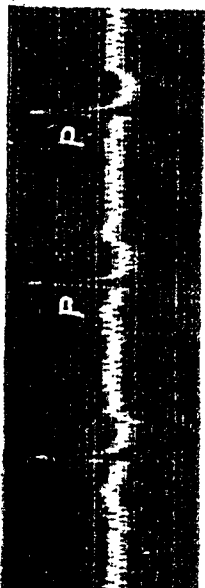
C-3/5



D-4/6



A-5/3



Flutter Caused by Quinidin. Six of our cases were the result of an endeavor to convert auricular fibrillation to a normal rhythm by quinidin. The mechanism of this reaction is well known and requires no further discussion in this paper.

Symptoms and Complications. The symptomatic results of auricular flutter vary greatly in different patients, depending upon such factors as the degree of cardiac disease; the ventricular rate, the duration of the flutter, and to some extent the nervous make-up of the patient. "Generally speaking the symptoms were those of a degree of heart failure with the special features of tachycardia added" (Parkinson and Bedford³¹).

The Rate of the Ventricles in Auricular Flutter. The symptomatology of flutter as we found it was roughly in direct proportion to the rate of the ventricles. With rates of 150 and over, the symptoms as a rule were quite marked; with the rate between 100 and 130, the symptoms were usually of slight or moderate severity; with slower rates, symptoms due to flutter *per se*, were practically absent. Usually there was noticeable improvement in the symptoms with lowering of the ventricular rate by treatment, or with conversion of flutter to fibrillation, or with the return of a normal rhythm. In those occasional instances where the ventricular rate equalled that of the fluttering auricle, there were usually profound disturbances, even unconsciousness.

Psychoses. Mental disturbances of varying degrees of severity were present in 10 of our cases. These occurred invariably with a high ventricular rate and with marked evidence of congestive heart failure. The onset of a psychosis would appear to be a grave prognostic sign, 4 of our 10 patients having died within 1 to 2 days and 2 within a week after its appearance. One recovered but died of heart failure 8 months later.

Embolism. This accident occurred in 5 of our patients. In 1, fibrillation was present at the time of the embolism while in another it occurred 3 days subsequent to the restoration of normal rhythm. In the three remaining instances, the accident occurred before the patients were admitted to the hospital, thus precluding our learning whether flutter was or was not present at the time of the accident. The weight of evidence indicates that embolism rarely if ever occurs during flutter. In the 9 cases recently reported by Parkinson and Bedford, flutter was not present at the time of the accident in any. It is of interest to note that 4 of Parkinson and Bedford's 9 cases of embolism and 3 of our 5 cases had mitral stenosis.

The Diagnosis of Auricular Flutter. Auricular flutter should be suspected in every regular tachycardia where the rate lies between 140 and 180 per minute. It must be differentiated from all varieties of paroxysmal tachycardia, from rapid simple tachycardia, and, when the ventricular response is irregular, as it not infrequently is, from auricular fibrillation. Only 2 of the various differential features will be discussed in this paper.

Vagal pressure* has been said to be particularly effective in increasing the degree of *A-V* block during auricular flutter. Parkinson and Bedford,³¹ however, do not believe that this occurs to any greater degree during flutter than during any other tachycardia except as it is caused by digitalis. It was possibly because most of our cases had received some digitalis that vagal pressure increased the degree of *A-V* block in a considerable number of them. The point that we wish to make is that the procedure has been of diagnostic help, not only clinically but electrocardiographically as well, and has enabled us to recognize a number of otherwise uncertain tachycardias definitely as flutter.

Hertz and Goodheart¹⁶ and Holmes and White¹⁷ have pointed out the value of fluoroscopy as a means of recognizing flutter and differentiating it from other tachycardias. The method has been helpful to us in an occasional case where the electrocardiogram left some doubt as to whether there existed a 2 to 1 flutter or a rapid auricular paroxysmal tachycardia. Observation of the auricles has at times enabled us to decide whether the rate of the auricles equaled or exceeded that of the ventricles.

The Auricular Rate in Flutter and Its Reaction to Drugs. The auricular rate in untreated flutter ranges between 220 and 370 per minute (Lewis²³). In our series, the lowest auricular rate recorded in an untreated case was 222 and the highest 334 per minute.

The Effects of Digitalis and Atropin on the Auricular Rate in Flutter. The direct muscular action and indirect vagal effect of digitalis on the auricular muscle are in conflict, with the vagal action usually predominating, and resulting in a slight increase in the rate of the auricular oscillations, through a shortening of the refractory period of the auricular muscle. From our various types of cases we have selected 9 which were receiving digitalis and carefully studied the auricular rate just preceding the change to fibrillation or normal rhythm. An increase in the auricular rate was observed in 4, no change in 2, and a decrease of the auricular rate in 3 of these cases. Parkinson and Bedford³¹ observed a decrease in the auricular rate in 5 and no change in 9 cases.

We did not study the effects of atropin in every case. We did administer the drug to several of our patients, and are citing the effects which were unexpected in one.

The expected effect of atropin on the auricular rate in flutter is slowing due to an increased refractory state, incident to vagal release; but occasionally there follows an increase (Wedd⁴⁶). Decrease in the auricular rate was the response we usually encountered.

One of our cases in which flutter followed large doses of digitalis showed a particularly anomalous response to both digitalis and atro-

* It would perhaps be more accurate to use the term carotid sinus pressure instead of vagal pressure.

pin in that the former slowed and the latter speeded the rate of the auricles. The auricular rate on the first day of flutter was 245. (Case 36, "Flutter Produced by Digitalis"). Digitalis was then stopped and 24 hours later, the auricular rate had fallen to 217 (Fig. 1).

The effects of atropin on the auricular behavior were also interesting (Fig. 2). On the first day of flutter, atropin sulphate, gr. $\frac{1}{25}$ hypodermically affected the auricular rate in the expected direction, slowing it from 245 to 240, 15 minutes after the injection, and to 226 at 30 minutes. On the second day of flutter, when the auricular rate was only 217, the same amount of atropin increased the auricular rate in 15 minutes to 237.

No definite explanation of such complicated reactions is justified perhaps. However, certain facts might be pointed out.

Why should the rate of the flutter have decreased from 245 on the first day to 217 on the second day of flutter? Inasmuch as digitalis had been discontinued 24 hours before the slower rate was recorded, the decrease might be attributed to removal of the vagal stimulating effects of digitalis and a resulting increase of the refractory state. This we have some hesitancy in doing because at the time of the slower auricular rate coupled ventricular extrasystoles had appeared and *T* wave changes and *A-V* block were of a higher degree, facts which suggest that digitalis action was more profound at the time of the slowed auricular rate (24 hours after the last dose of digitalis).*

If it can be justifiably assumed that digitalis was more strongly affecting the heart at this time, the slowed auricular rate might conceivably have been due to a predominant direct effect of the drug upon the muscle with a resulting increase in the refractory period. This as well as the preceding hypothesis is rendered unlikely by the conspicuous increase in the auricular rate caused by atropin on this day. This result of vagal release leads us to feel that the slowing of the auricular rate, although it was recorded 24 hours after the last dose of digitalis, was in the main the result of vagal stimulation. We know of no established and accepted action of atropin except preliminary vagal stimulation and ultimate release.†

* We have on several occasions seen the maximum effects of digitalis manifested as long as 24 hours after its last administration.

† Wedd⁴⁶ has mentioned stimulation of the sympathetics as a possible explanation of an increase in the auricular rate under atropin.

FIG. 2.—Effects of Atropin on Auricular Rate. Flutter with *A-V* dissociation. Strip 1: Flutter with 6 to 1 block (duplicate of *C*, Fig. 1). Strip 2: Fifteen minutes after atropin sulphate, $\frac{1}{25}$ gr., hypodermically; auricular rate, 237; ventricular rate, 97; ventricular impulses are independent of auricular impulses. Strip 3: Thirty minutes after atropin: auricular rate, 222; ventricles responding regularly to every second auricular impulse. Strip 4: Second day of flutter (duplicate of *D*, Fig. 1): auricular rate, 237. Strip 5: Fifteen minutes after atropin sulphate, $\frac{1}{25}$ gr., hypodermically; auricular rate increased to 242; ventricular complexes perfectly regular and independent of auricular beats.

That vagal release and not stimulation was the action of atropin at the time is indicated by the great improvement in *A-V* conduction that accompanied the increased auricular rate. (Fig. 2).

Lewis, Drury and Bulger²⁷ found that vagal stimulation, after speeding the auricular rate up to a point, might then lead to irregularity and often sudden cessation of the flutter through its action in removing the state of partial refractoriness more effectively than it shortened the absolute refractory period. We have no clear conception how vagal stimulation could slow the auricular rate in our case. Conceivably, an interplay of the effects of vagal stimulation on the partial and absolute refractory states might have driven the wave into longer pathways and thus perpetuated the flutter at a slower rate.

In the preceding discussion we have given no consideration to the seriously poisoned condition of the heart. This fact might easily modify any reaction and makes any explanation of the results largely hypothetical.

A-V Dissociation in Flutter Caused by Atropin. During the 2 days that flutter existed, it was associated with high-grade *A-V* block, being initially 6 to 1 and progressively increasing to 8 to 1 and even 12 to 1. On both days, atropin sulphate, gr. $\frac{1}{25}$, hypodermically, led to a dissociation of the auricular and ventricular mechanisms, a behavior that we have not seen described during auricular flutter (Fig. 2.). On the first day, the auricular rate at the time of dissociation, was 237 and the ventricular 97; on the second day, 15 minutes after atropin, the rates were respectively 242 and 94. The ventricular beats bore no relation to auricular impulses and almost certainly arose in junctional structures. On the first day, the ventricles were slightly irregular, but their perfect regularity on the second day makes the mechanism beyond question an *A-V* dissociation. This disorder was transient; 30 minutes after the atropin the ventricles were responding regularly to every second auricular impulse.

This dissociation is probably analogous to that observed by Wilson⁴⁹ in normal rhythm where the disturbance either appeared spontaneously after atropin, or was induced by vagal pressure in the period 8 to 15 minutes after its injection. The probable cause during sinus rhythm is a selective action of atropin on the vagal endings in the *A-V* node, Wilson⁴⁹ believing the effective action to be release, Lewis²³ stimulation. In our case dissociation was probably the result of the combined effect of digitalis and atropin and not of the latter alone.

Quinidin. This drug always slowed the auricular rate of the cases of our series to which it was administered.

The Effect of Digital Stimulation of the Vagus Nerve on Auricular Flutter. Under experimental conditions, flutter in dogs can at times be ended or converted into fibrillation through the application

of electrical stimulation to the exposed vagus nerve.^{26,37} As far as we are aware, digital stimulation of the unexposed vagus has never been reported to have ended flutter in man, though it has been observed to affect the rate^{3,22,38,50} In 1 case, we apparently did transform auricular flutter into fibrillation by applying pressure over the vagus nerve in the neck. Lewis²³ has stated that vagal stimulation sufficiently intense to affect flutter greatly is not likely to be obtained by pressure over the carotids. However, we see no convincing reason why this response might not occasionally occur.

The patient, F. B., aged 45 years, entering the hospital for bilateral herniorrhaphy was unaware of any cardiac derangement. However, a routine examination revealed a history of slight breathlessness at rest, questionable enlargement of the heart, a soft apical systolic murmur, a normal blood pressure, and a heart rate of 150, which the electrocardiograph showed to result from auricular flutter. While pressure was being applied over the right carotid the rhythm changed to auricular fibrillation (Fig. 3). The latter rhythm continued for 2 days and then spontaneously reverted to normal. He was followed at intervals until his death 2½ years later, without flutter ever again being observed.

There is of course the possibility that the change from flutter to fibrillation was spontaneous and not the result of vagal pressure. We attribute the change to vagal stimulation largely because of the behavior of the auricular rate and because of the experimental results of vagal stimulation in dogs that have already been referred to. For purposes of accuracy in measurement, we have used the intervals between two auricular cycles for comparison. The rate did not begin to speed demonstrably until 7 double cycles before the onset of fibrillation. The interauricular cycle lengths in seconds for these last 7 double cycles are recorded in Table 3.

TABLE 3.—EFFECT OF VAGAL PRESSURE ON THE AURICULAR RATE.

Cycles.	Time, seconds.
A	0.362
B	0.358
C	0.358
D	0.355
E	0.365
F	0.346
G	0.343

The auricular rate speeded progressively for 4 double cycles, then lengthened for 1 double cycle and then again progressively speeded for the next 2, at which point frank fibrillation supervened.

Lewis, Drury and Bulger²⁶ found that vagal stimulation speeded experimental auricular flutter regardless of whether the rate of fiber conduction was nearly normal or was slowed: in the first instance, by shortening the absolute refractory period and thus opening shorter pathways to the circulating wave; in the second instance,

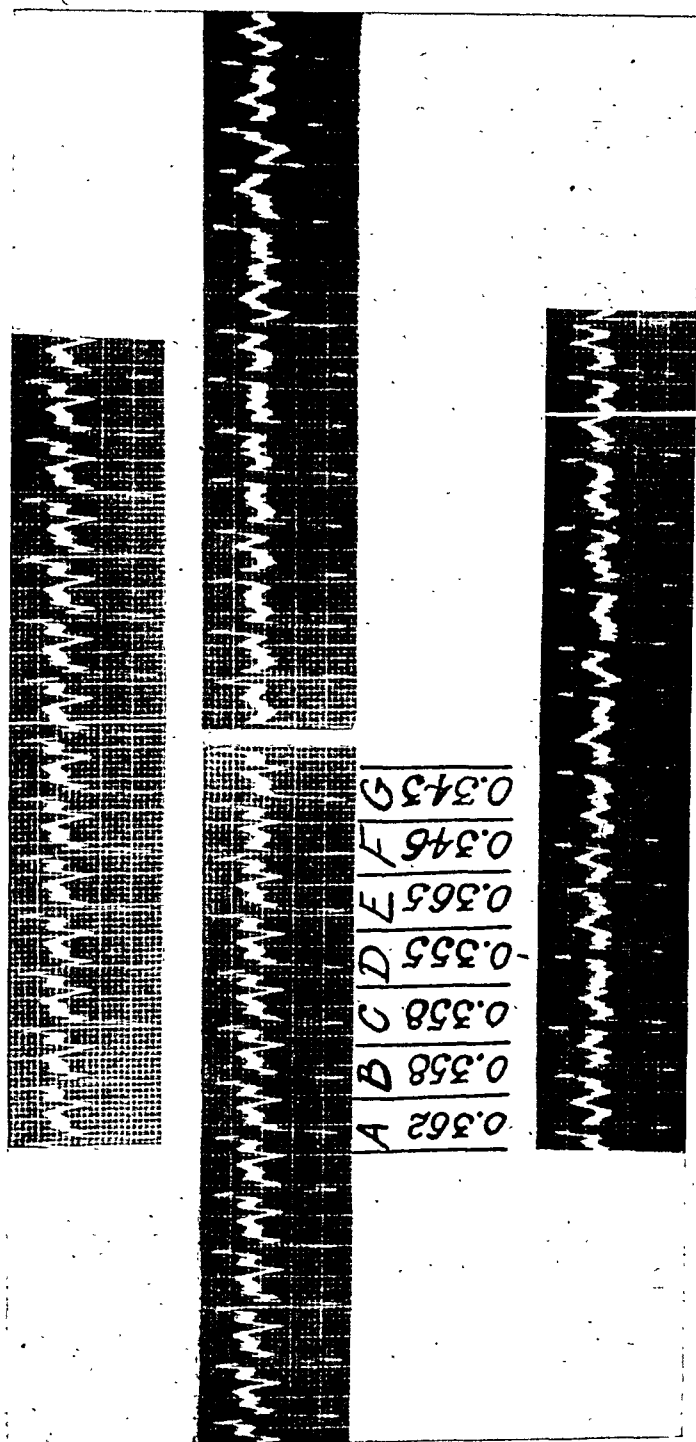


FIG. 3.—Flutter converted to fibrillation by vagal pressure. All strips are continuous and were separated only for purposes of mounting. First line shows: 2 to 1 flutter. White line is signal indicating vagal pressure. Second line, first half shows speeding of auricles. Measured intervals refer to auricular cycles. Just at the separation of the tracing, auricular flutter changed to fibrillation. Third line shows continuation of fibrillation. White line marks release of vagal pressure.

by removing the island of refractory muscle in the path of the wave—an effect chiefly on the state of partial refractoriness rather than the absolute refractory period. Either of these effects resulted in a gradual progressive rise in the auricular rate. If the effect was disproportionately greater on the partial than on the absolute refractory state, the flutter might become somewhat irregular and often suddenly end. If the two effects balanced each other, flutter would continue.

These authors²⁶ found that the change from flutter to fibrillation when it occurred during vagal stimulation was accomplished in most instances at least through an intermediary state of rapid reëxcitation. This disturbance could be detected in ordinary tracings obtained from limb leads. In our clinical case, such an intermediary stage seems most improbable. At any rate, there are no suggestions of such a disturbance in the tracings.

In a case reported by Wilson⁵⁰ in which ocular pressure conspicuously increased the rate of flutter, the speeding was attributed to a shortening of the path of the wave. In our case, the subsequent change to fibrillation suggests that the increased rate during vagal stimulation resulted from the same cause. The only thing that makes this at all doubtful is the sudden slowing in the progressive increase in the rate of Cycle E. It is to be remembered, however, that the measured intervals refer to double cycles. Apportioned between 2 cycles, the slowing would not be great: perhaps not sufficiently so to deter us from saying that the increase in rate was an orderly progressive one.

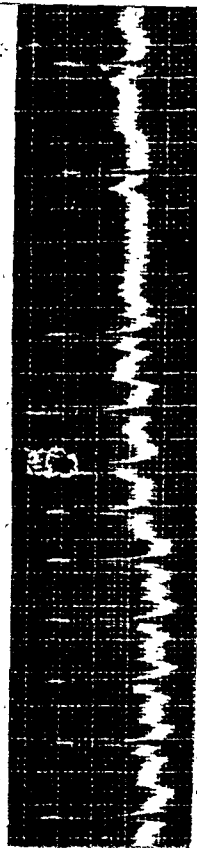
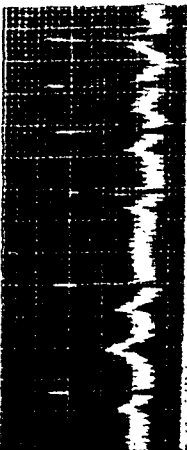
Onsets and Offsets of Auricular Flutter. Neither the start nor the termination of periods of auricular flutter have been recorded very frequently in electrocardiograms. We have been able to find either one or the other of these events reported in five papers.^{23, 32, 41, 43, 52}

In most of the cases reported the flutter was impure.⁵² In some of the paroxysms, premature auricular beats appear to have initiated them;⁵² in others, no such preliminary disturbances occurred; the offsets happened abruptly or were either preceded by a slowing of the auricular rate or occasionally by slight auricular speeding.

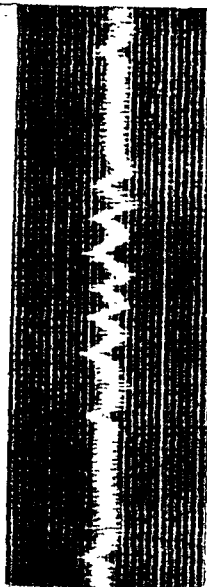
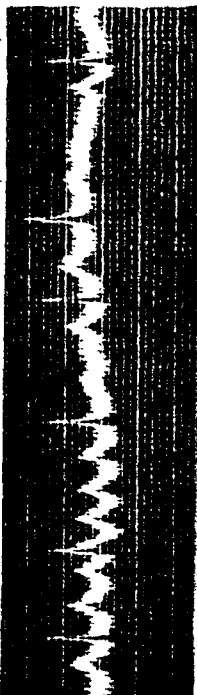
We observed onsets in 4 patients and offsets in 5. In all of these cases the flutter was impure at best and usually approached auricular fibrillation.

In patient, A. R. (Fig. 4, line 1), the onsets invariably were precipitated either by exercise or by premature auricular beats. Toward the end of the paroxysm illustrated, the auricular waves are fairly regular in time and also in shape except as the irregularity of the ventricular responses modifies them. The last 2 cycles, each 0.198 second in duration, while not slower than some individual cycles, are definitely slower than the immediately preceding ones. The preceding 7 cycles are impossible to measure accurately; measured *in toto* and averaged, each has an estimated duration of 0.188

Case A.K.

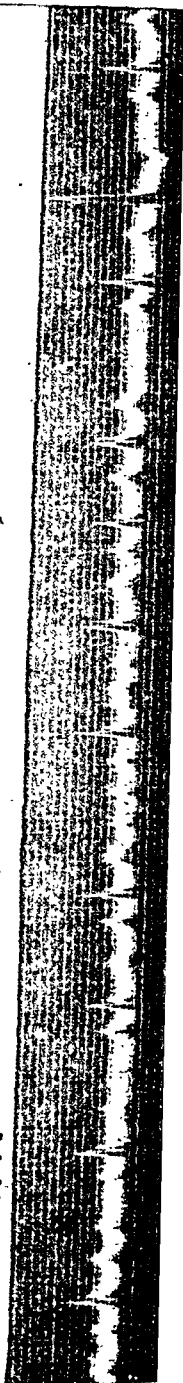


Case W.K.



Case E.W.

0.205
0.184
0.153
0.147
0.192



second. Such slight and uncertain changes do not warrant the definite conclusion, but suggest that the termination of flutter was preceded by slowing of the auricles.

In patient, W. K. (Fig. 4, second line), premature auricular beats were also present and at times initiated paroxysms; at other times, onsets were spontaneous. Both types of onsets are illustrated. The behavior of the auricular rate at the time of offsets was inconsistent. In 3, the last cycle while not longer than some individual cycles, was slower than the cycle immediately preceding it; in the fourth offset studied, the last cycle was definitely faster than the preceding one. One of each variety of offset is shown.

In patient, E. W., the flutter was definitely impure. The flutter waves closely approach in shape the *P* and *T* waves, and therefore make it difficult to be certain of the exact point of offset. In the first short paroxysm (Fig. 4, third line, marked "x"), the last auricular wave is definitely faster than the preceding wave. The exact point of the other offset illustrated is uncertain. There are numerous premature beats, but we cannot be certain that any of these impulses actually initiated period of flutter.

In both of our other cases (not illustrated in Fig. 4), the flutter was impure. Both offsets (seen in both) and onsets (seen in one) were spontaneous and no change in the auricular rate preceded the termination of the flutter.

Other Disturbances of Rhythm Associated with Auricular Flutter.
Flutter with Aberrant Ventricular Complexes. During rapid auricular beating, aberration of the resulting ventricular complexes is not uncommon. Among our 65 cases, we found widened ventricular complexes in ten instances. In two, the widening was present at a high ventricular rate only, the ventricular complexes returning to their normal width when the rate slowed. In one of these the aberration was definitely a toxic quinidin effect, the finding disappearing with the elimination of the drug. The 8 hearts with permanent bundle-branch disturbance did not tolerate flutter any worse than did hearts similarly diseased but without intraventricular block. In 7 of these, normal rhythm was restored and persisted for a considerable period. On the other hand, our 1 patient who developed bundle-branch disturbance incident to a rapid ventricular rate did do very badly and died soon after the appearance of aberration.

A-V Heart Block and the Ventricular Rate in Flutter. When they first came under observation and before treatment was instituted 36 of our patients had 2 to 1 block and 11 showed a combination of 2 to 1 and 3 to 1 block. The remainder showed either higher grades of block or changing *A-V* ratios, resulting presumably from digitalis, which had been used in small amounts.

The ventricular rates lay between 150 and 185 in 28 and between 111 and 149 in 32 cases. In only 6 was the rate at the initial observation below 100. In 4 of these digitalis had been administered and

was probably the cause of the increased *A-V* block and consequent slow ventricular rate. Only 2 patients, Case 62, with an *A-V* ratio of 3 to 1 and a ventricular rate of 88, and Case 51, with a ventricular rate of 36, the result of permanent complete *A-V* heart block, showed a ventricular rate below 100 where digitalis could be positively eliminated as a factor.

Complete A-V Heart Block Associated with Auricular Flutter. Parkinson and Bedford³¹ reported 1 case of their own and were able to find in the literature but 8 other examples of the association of complete *A-V* block and flutter.^{2, 9, 14, 19, 36, 40, 45, 51} Our 1 patient who showed this combination of disturbances was a man of 65 with evidences of arteriosclerotic heart disease. Various attempts to effect the *A-V* block were always unsuccessful. This case will not be further considered here as it is being separately reported in connection with histologic and other electrocardiographic findings.

Ventricular Tachycardia in Association with Flutter. This combination is undoubtedly but rarely seen. We could find in the literature but 1 clear case of an association of these arrhythmias, a case reported by Gallavardin.¹² In 2 of our cases, these arrhythmias were associated; both had received toxic doses of digitalis. Inasmuch as these cases are being reported in another paper, they will not be further referred to here.

Flutter with 1 to 1 Ventricular Response. This disturbance usually manifests itself as a brief affair during ordinary 2 to 1 flutter. The two examples of this that we have seen, both accompanied by alarming symptoms, have been previously reported.²⁹ Parkinson and Bedford³¹ in reviewing the literature of flutter have accepted 18 of the reported cases as genuine examples of 1 to 1 flutter. To this number should be added the case recently reported by Fuller.¹¹

The Treatment of Auricular Flutter. Prior to the introduction of quinidin, digitalis was the only drug available for the treatment of auricular flutter. Quinidin while in no way supplanting digitalis, has nevertheless proved itself to be a drug of great value.

The Results of Treatment. Since the introduction of quinidin there are now available three methods of treating auricular flutter: (a) Digitalis, (b) quinidin, and (c) a combination of digitalis and quinidin, the latter being used to end fibrillation after the former has induced this rhythm. Of these methods, the best results have been obtained by the use of digitalis alone or by its combination with quinidin.

In the series of 52 cases collected by Ritchie³⁵ normal rhythm was restored in 23 (44.7 per cent) by digitalis. In the 52 cases of Parkinson and Bedford,³¹ 20 cases were treated by digitalis alone: the results were a restoration of normal rhythm in 9 (40 per cent), permanent fibrillation in 4, nodal rhythm in 1, and a persistence of flutter in 5 cases. Quinidin alone was used in 15 instances of established flutter, successfully restoring a normal rhythm in 3,

and failing in 12. In 6 cases in which persistent fibrillation had been produced by digitalis, quinidin restored and maintained normal rhythm in 3 and caused return of flutter in 3. Of their 40 cases with established flutter, a return to normal rhythm followed the use of digitalis or quinidin, either alone or in combination in 20 cases, or 50 per cent.

The results in our series of 65 cases are tabulated in Tables 1 and 2. Considering all of our 65 cases, both the established and paroxysmal forms and those due to drugs, normal rhythm either returned spontaneously or was restored by drugs in 43 (66.1 per cent) of the 65 cases. An additional 4 cases, or 6 per cent were changed from flutter to permanent fibrillation. The total percentages therefore in which the flutter was transformed either to normal or to permanent fibrillation was 72.2. It seemed to us that the best idea of the efficacy of the various available forms of treatment could be gotten if the 19 cases that were either paroxysmal or the result of drugs or untreated were omitted and the remaining 43 cases of established flutter were considered. Of the 43 cases of established flutter which received treatment, normal rhythm was restored by digitalis alone 24 times, by quinidin alone 3 times, by digitalis and quinidin combined 4 times and by vagal pressure once. The total, therefore, is 32 successes out of 43 attempts to restore normal rhythm, a successful percentage of 74.4. Of the 11 cases, in which normal rhythm was not restored, 4 left the hospital with permanent fibrillation, only 1 of the 4 having received any quinidin, and this in inadequate amounts, and 7 cases continued to flutter, digitalis and quinidin both having been used, however, in only 2, the remaining 5 having received digitalis only. It seems not improbable that our successful percentage may have been considerably increased had all of these 11 cases received adequate amounts of quinidin after the digitalis had failed.

In securing a return to normal in 66.1 per cent of all varieties of flutter (established, paroxysmal, and those due to drugs), in 74.4 per cent of our treated cases of established flutter, in 55.8 per cent of our cases of established flutter treated by digitalis alone, and in 60 per cent of the cases treated by quinidin alone, we have apparently been unusually fortunate.

We have devised no definite routine of treatment. Our procedure has been first to use digitalis alone. Usually we have given approximately 3 drams of the tincture daily for 2, 3, or even 4 consecutive days, the duration of this period of large dosage depending upon the condition and size of the patient and the need of hurry. After such a period, the dose of digitalis has been reduced to 1 dram per day and continued in this amount until we even secured a change of rhythm or until evidences of toxicity have either appeared clinically or been revealed by the electrocardiograph.

The successful abolition of flutter often requires several times the Eggleston dose of digitalis. Such quantities are obviously dangerous and should only be used with rigid observation. While we have frequently disregarded such clinical symptoms as loss of appetite and nausea, the development of coupled extrasystoles, hitherto not present, is a sign that we now never ignore. These, even if very occasional ones, are to us a positive indication for abandoning the use of digitalis in treating auricular flutter.

In spite of the use of such large amounts of digitalis, we have had but one fatality that could be attributed to the drug. Warnings to discontinue the digitalis appeared in ample time, but through an error, only the day order was stopped and a fairly large amount being given at night was continued. This led to ventricular tachycardia and death. In one other instance, we ignored the development of occasional coupled extrasystoles and continued the drug one day after their appearance. Ventricular tachycardia resulted, but fortunately disappeared in 24 hours and nothing came of the episode.

When forced to abandon digitalis, after a few days wait, we have begun quinidin. After a preliminary dose of 4 grains, the patients have been put on 4 grains 5 times a day, 4 doses being given during the waking hours and 1 at 2 A.M. If this had no effect in 3 days, the dose was increased to 5 grains 5 times a day, then after 3 days, to 6 grains 5 times a day, and so on until 40 grains a day were being administered. Usually, we have gone no further than this. Occasionally, however, we have given higher amounts, once reaching the large dosage of 81 grains per day. In this particular instance, the patient was in severe cardiac failure with flutter. The appearance of coupled ventricular extrasystoles forced us to abandon digitalis. Quinidin in the large amounts mentioned caused a return of normal rhythm and restored the heart to a degree that was compatible with a relatively normal life.

The only justification for taking the risk that the administration of such large amounts of digitalis and quinidin entails, lies in the urgent necessity of abolishing flutter. If the need is not urgent, we do not advocate taking the risk. If it is, we do.

When digitalis has successfully transformed flutter into fibrillation, we now wait no longer than 1 week for spontaneous return to normal rhythm, but begin the use of quinidin. It is our experience that the sooner this drug is begun, the more apt are we to secure a return to normal rhythm.

Quinidin, at least theoretically, should prove of great value in the treatment of paroxysmal flutter, both in shortening the paroxysms and in diminishing their frequency. Parkinson and Bedford³¹ observed both of these results. We have not sufficiently observed our cases of paroxysmal flutter or been able to keep them under sufficiently careful observation after their discharge from the hospital to speak from our own results on this phase of the subject. In

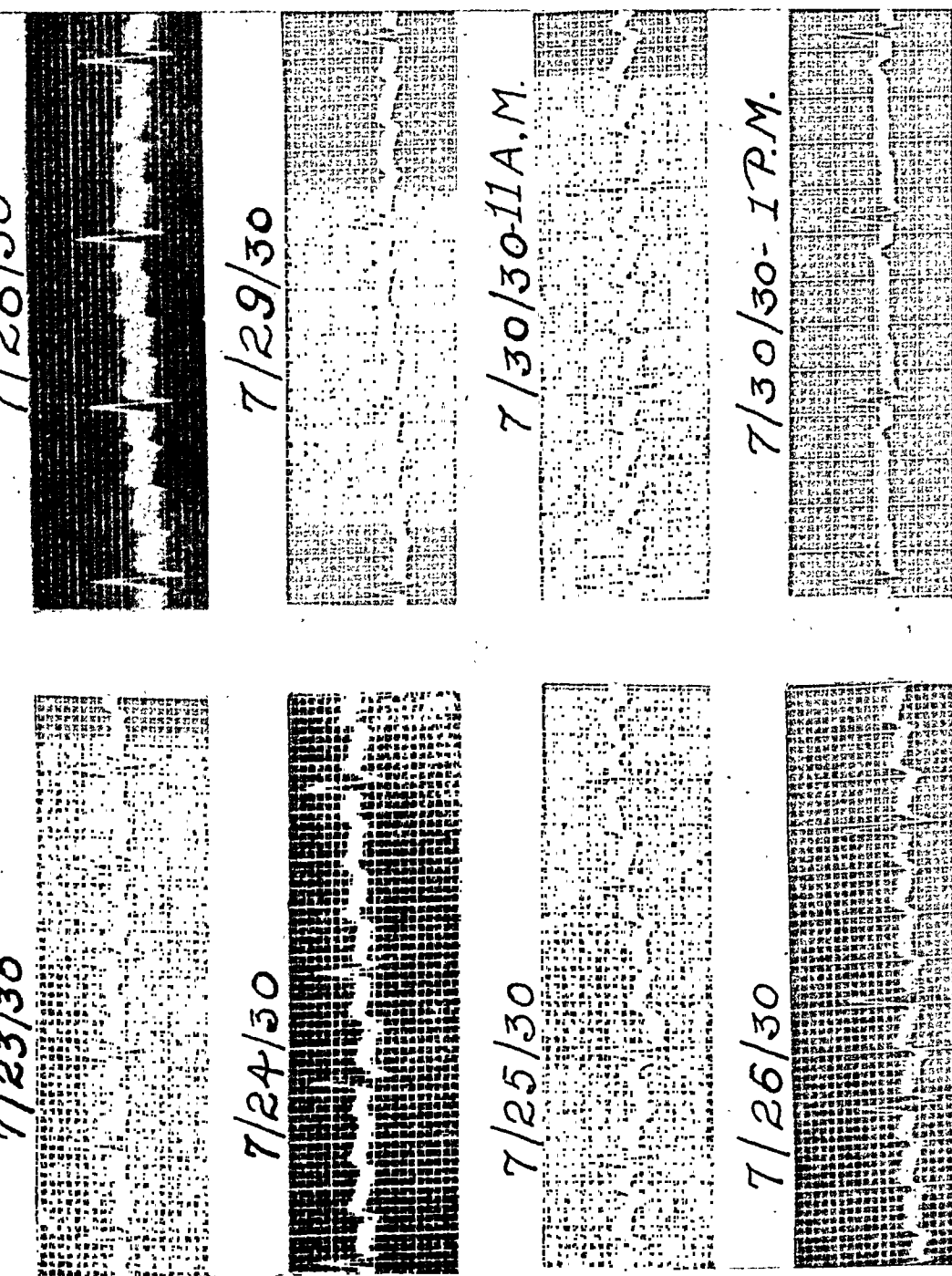


FIG. 5.—Shows the changes in auricular rate under digitalis in a case of auricular flutter that apparently returned to normal without fibrillating. The exact time intervals and the auricular rates are referred to in the text.

2 cases, we did obtain what we thought was distinct benefit from quinidin in lessening the frequency of the paroxysms.

The Conversion of Flutter to Normal by Digitalis without an Intervening Stage of Fibrillation. It is usually assumed that digitalis abolishes flutter by first transforming it into fibrillation. Eleven of our 43 cases of established flutter were returned to normal without an observed period of auricular fibrillation. Parkinson and Bedford³¹ encountered the same phenomenon though they do not state how many times.

This has led us to wonder if digitalis may not fairly frequently convert flutter to normal directly without an intermediary stage of fibrillation. There are theoretical and experimental reasons for believing that it might. In all of our 11 cases, it is of course conceivable that the auricles did fibrillate briefly between the period of flutter and normal rhythm, inasmuch as the change was never recorded on the electrocardiograph. In one of our cases, the period of possible fibrillation could not have exceeded 2 hours: a tracing taken at 11 A.M. showed flutter while one taken at 1 P.M. revealed a normal rhythm.

The behavior of the auricular rate in these cases was inconstant: in some, it was tending to speed in the last tracing taken before normal rhythm returned while in others it was either slowing or unchanged. The auricular rates in the case just referred to in which any period of fibrillation seems unlikely are shown in Table 4.

TABLE 4.—BEHAVIOR OF AURICULAR RATE PRECEDING THE CHANGE FROM FLUTTER TO NORMAL.

Date.	Interauricular cycle lengths,* seconds.	Rate per minute.
July 23	0.205	293
July 24	0.209	287
July 25	0.2024	296.4
July 26	0.200	300
July 28	0.208	288
July 29	0.200	300
July 30, A.M.	0.2075	289
July 30, P.M.	Normal rhythm	

* These figures were determined with a comparator. The direction of the changes in rate, however, was perfectly obvious grossly.

From the history of this patient we judge the onset of flutter to have occurred 3 weeks before admission. After preliminary electrocardiograms, the administration of tincture of digitalis was begun, 10 drams in all being administered in 8 days.

There was first a definite increase in the auricular rate, then slowing (July 28, 1930), then speeding, and finally definite slowing 2 hours before normal rhythm was observed. The slowing would fit in with either of two possible explanations. First, a predominance of the direct effects of the drug by causing intra-auricular block might prevent further reëtrance of a circulating wave. Second,

TABLE 5.

Total	65
Caused by digitalis	2
Caused by quinidin	5
	— 7
	58
Untreated	3
	— 55
Paroxysmal	12
	— 43
Normal rhythm restored:	
(a) By digitalis alone	24
(b) By quinidin alone	3
(c) By digitalis plus quinidin	4
(d) Vagal pressure	1
	— 32
	11
Transformed in fibrillation	4
	— 7
Failures	7

TABLE 6.

Case.	Amount of drug.	Days.	Result.
1	120 gr.	10	No change; death.
2	7 dr.	8	Fl. to N.R.
3	33 dr.	33	No change; death.
	297 gr.	23	
4	6½ dr.	10	Fl. to Fib. to Norm.
5	19½ dr.	23	Changed to Fib.
6A	42 dr.	57	Fl. to Fib.
6B	57 dr.	19	No change; death.
7	144 In., 2 Tr.	20	No change; death.
8	5 dr.	10	No change.
9	6 dr.	4	No change.
10	2 dr. Tr., 1/200 gr.	7	Fl. to Fib. to Norm.
	Stroph.		
11	7½ dr.	3	Fl. to Fib. to Norm.
12	5½ dr.	12	Fl. to Fib. to Norm.
	12 gr.		Fl. to Norm. spont.
13	7 dr.	7	Fl. to Norm.
14	16 dr.	18	Fl. to Fib.
	10 gr.		Fib. to Norm.
15	19 dr.	16	No effect.
	288 gr.	12	No effect.
16	7 dr.	6	Fl. to Norm. in 5 days.
17	10½ dr.	14	Fl. to Fib. to Norm.
18	4½ dr.	4	No change.
19	23½ dr.		
	60 gr.	11	Fl. to Norm.
20	35 dr.	9	Fl. to Norm. V.P.T.
21	13 dr.	13	Fl. to Norm.
22	28 dr.	21	No change; drug stopped.
23	6½ dr.	8	Fl. to Fib.
	5 gr.		Fib. to Norm.
24	23½ dr.	21	No change; insuff.
25	¾ dr.	1	Fl. to N.R. (paroxysmal).
26	5¼ dr.	7	Fl. to Norm.
27	30 dr. Inf., 7 Tr.	7	Fl. to Norm.

TABLE 6.—(Continued.)

Case.	Amount of drug.	Days.	Result.
28	None		Died.
29	326 gr.	18	Fl. due to Quin.
30	16½ dr.	24	Fl. to Norm.
31	8 dr.	3	Fl. to Fib.
	60 gr.	2	Fib. to Norm.
32	6 dr.	5	Fl. to Fib.
33	7 dr.	1	Fl. to Fib. to Norm.
34	11 dr.	8	Fl. to Fib. to Norm.
35	12½ dr.	6	Fl. due to digitalis.
36	24 dr.	8	Fl. due to digitalis.
37	3½ dr.	4	Fl. to Fib. by vagal pressure.
38	8 dr.	4	Fl. to Norm.
39A	?	?	Fl. to Norm.
39B	12 dr.	24	No change.
40	10½ dr.	7	Fl. to Fib. to Norm.
41	18½ dr.	11	Fl. to Fib.
	12 gr.	1	Fib. to N.R.
42	120 gr.	8	Fl. due to Quin.
43	2 dr.	2	Fl. to N.R. (paroxysmal).
44A	8 dr.	18	Fl. to Fib. to Fl.
	576 gr.	52	Fl. to Norm.
4B	1004 gr.	31	Fl. to Norm.
45	20 dr.	14	Fl. to Fib. to Norm.
46A	54 dr.	30	No change.
	750 gr.	9	Fl. to Norm.
46B	44 dr.	19	No change.
	172 gr.	7	Fl. to Norm.
47	4 dr.	3	Fl. to Fib. to Norm.
48	29½ dr.	12	Fl. to Fib.
49	4 dr.	4	Fl. to Norm.
50	4½ dr.	3	Fl. to Norm.
51	6 dr.	?	Fib. to Fl. to Fib. (digitalis?)
52	7½ dr.	6	Fl. to N.R.
53	12½ dr.	7	Fl. to Fib.
54A	18 dr.	15	Fl. to Fib.
	30 gr.	2	Fib. to N.R.
54B	20 dr.	14	Fl. to N.R.
55	35 ⅝ dr.	49	Fl. to Fib.
56	20½ dr.	18	Fl. to Fib. to N.R.
57	5 dr.	4	No change.
58	None	..	No change.
59A	27 dr.	17	Fl. to Fib.
59B	8 dr.	5	Fl. to N.R.
60	12 dr.	9	Fl. to Fib.
61	9 dr.	9	Fl. to N.R.
62	2½ dr.	3	Fl. to N.R. (paroxysmal).
63	10 dr.	15	Fl. to Fib.
	400 gr.		
64	9 dr.	5	Fl. to Fib. to N.R.
65	Well digitalized	5	Fl. to N.R.
	138 gr.		

dr. = drams of tincture of digitalis.

gr. = grains of quinidin sulphate.

Stroph. = strophanthin.

Fib. = fibrillation.

Fl. = flutter.

N.R. = normal rhythm.

Norm. = normal rhythm.

A and B refer to different courses of treatment.

Lewis, Drury and Bulger²⁶ found that vagal stimulation alone can end flutter under experimental conditions. An interplay of the vagal action on the partial and absolute refractory state, they found, could first speed, then slow the rate of the auricle, and finally abruptly end the flutter. The behavior of the auricular rates in our case might conceivably be due to such an interaction, which might finally have led to a closure of the gap of responsive muscle and an immediate return to normal rhythm. The weight of observation is not against such a predominance of the vagal effect of digitalis.

We must let the matter rest here. It appears to us to be possible for digitalis by either of its influences on the auricular muscle to end flutter without first changing it to fibrillation. None of our cases show positively that this was the method of change though some of them—1 in particular—suggest rather strongly that it may have been.

Summary. A series of 65 cases of auricular flutter is reported, 12 of which were classed as paroxysmal and 43 as established flutter. Seven were due to drugs and 3 received no treatment and were therefore unclassified.

These cases include:

(a) Two instances of flutter apparently produced by toxic amounts of digitalis. One of these cases showed ventricular tachycardia in association with flutter.

(b) One case of complete heart block (not due to digitalis) associated with auricular flutter.

(c) A case of auricular flutter apparently transformed into auricular fibrillation by digital pressure on the vagus nerve in the neck.

(d) Five cases in which onsets or offsets of brief paroxysms of impure flutter occurred.

(e) A case in which *A-V* dissociation followed the injection of atropin in a person severely overdigitalized.

The effects of digitalis upon the auricular rate are discussed.

The results of treatment of the disturbance were quite successful. Of the entire 65 cases (established, paroxysmal, and those due to drugs) a return to normal rhythm was secured in 66.1 per cent. Considering only the cases of established flutter, normal rhythm was successfully restored in 74.4 per cent of the cases.

The method of choice in this series of cases was the use of digitalis until fibrillation was established. Digitalis was then discontinued, and unless a normal rhythm had spontaneously returned within a week, the administration of quinidin was begun. The latter drug was used alone after digitalis had either failed to bring on fibrillation or had brought on certain toxic manifestations which rendered a further use of digitalis inadvisable.

BIBLIOGRAPHY.

1. Billings, F. T.: Subdiaphragmatic Pain of Cardiac Origin, *Ann. Clin. Med.*, 1923, 3, 174.
2. Blackford, J. M., and Willius, F. A.: Auricular Flutter, *Arch. Int. Med.*, 1918, 21, 147.
3. Clerc, A., and Bascouret, M.: The Effect of Vagal Excitation by Means of Ocular Compression Upon Auricular Flutter in Man, *Arch. d. mal. du coeur*, 1926, 19, 581.
4. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exp. Med.*, 1924, 39, 1.
5. Cushny, A. R., and Edmunds, C. W.: Paroxysmal Irregularity of the Heart and Auricular Fibrillation, *Am. J. Med. Sci.*, 1907, 133, 67.
6. Cushny, A. R.: Digitalis and Its Allies, Longmans, Green & Co., London, 1925.
7. Dameshek, W.: The Heart in Hyperthyroidism, *Boston Med. and Surg. J.*, 1924, 190, 187.
8. Danielopolu, D.: Arrhythmia complete chez l'homme provoqué par le digitale, rôle du système modérateur, *Compt. rend. Soc. de biol.*, 1916, 79, 97.
9. Donzelot, E., and Pezzi, C.: Tachysystole de l'Oreille avec dissociation atrio-ventriculaire complete, *Bull. et mém. Soc. de hóp. de Paris*, 1914, 37, 497.
10. Drury, A. N.: Arborization Block, *Heart*, 1921, 8, 20.
11. Fuller, A. B.: A Case of Auricular Flutter with Paroxysmal Attacks of 1 to 1 Response of the Ventricles, *Am. Heart J.*, 1927-1928, 3, 735.
12. Gallavardin, L.: Tachycardia ventriculaire terminée, *Arch. d. mal. du coeur*, 1920, 13, 210.
13. Gilchrist, A. R.: Paroxysmal Ventricular Tachycardia, *Am. Heart J.*, 1925, 26, 646.
14. Hall, D.: Five Cases of Auriculo-ventricular Bundle Branch Block, *British Med. J.*, 1924, 1, 778.
15. Hamberger, W., Priest, W. S., and Bettman, R. B.: Experimental Coronary Embolism, *Am. J. Med. Sci.*, 1926, 171, 168.
16. Hertz, A. F., and Goodhart, G. W.: The Speed Limit of the Human Heart, *Quart. J. Med.*, 1908-1909, 11, 213.
17. Holmes, G. W., and White, F. D.: Auricular Flutter Detected by the Fluoroscope, *J. Am. Med. Assn.*, 1917, 681, 844.
18. Hume, W. E.: A Polygraphic Study of Four Cases of Diphtheria with a Pathological Examination of Three Cases, *Heart*, London, 1913-1914, 5, 25.
19. Keating, J. H., and Hazek, J.: Auricular Flutter with Report of Cases, *Am. J. Med. Sci.*, 1922, 164, 398.
20. Kerr, W. J., and Hensell, G. C.: Observation of the Cardiovascular System in Thyroid Disease, *Arch. Int. Med.*, 1923, 31, 398.
21. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goiter, *Am. J. Med. Sci.*, 1917, 154, 834.
22. Levine, S. A., and Frothingham, C.: A Study of a Case of Auricular Flutter, *Arch. Int. Med.*, 1915, 16, 18.
23. Lewis, T.: Mechanism and Graphic Representation of the Heart Beat, Shaw and Sons, London, 1925.
24. Lewis, T.: Observations Upon a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle "Auricular Flutter," *Heart*, 1912-1913, 4, 171.
25. Lewis, T.: The Mechanism of the Heart Beat with Special Reference to Clinical Pathology, Shaw and Sons, London, 1925, p. 311.
26. Lewis, T., Drury, A. N., and Bulger, H. A.: Observations Upon Flutter and Fibrillation. Part VI. The Refractory Period and the Rate of Propagation in the Auricle, Their Relation to Block in the Auricular Walls and to Auricular Flutter, *Heart*, 1921, 8, 83.
27. Lewis, T., Drury, A. N., and Bulger, H. A.: Observation on Flutter and Fibrillation. Part VII. The Effects of Vagal Stimulation, *Heart*, 1921, 8, 141.
28. McKenzie, J.: Digitalis, *Heart*, 1910-1911, 11, 273.
29. McMillan, T. M., and Sweeney, J. A.: Auricular Flutter with 1 to 1 Ventricular Response, *Am. J. Med. Sci.*, 1924, 168, 893.
30. Neuhoff, S.: Auricular Flutter Accompanying Acute Endopericarditis, *Med. Rec.*, 1915, 88, 995.
31. Parkinson, J., and Bedford, D. E.: The Course and Treatment of Auricular Flutter, *Quart. J. Med.*, 1927, 21, 21.

32. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, *Heart*, 1915-1917, **6**, 27.
33. Parkinson, J., Gosse, S. H., and Gunson, E. B.: The Heart and Its Rhythm in Acute Rheumatism, *Quart. J. Med.*, 1919-1920, **13**, 363.
34. Resnick, W. H.: Transient Auricular Fibrillation Following Digitalis Therapy with Observations on the Action of Atropin, *J. Clin. Invest.*, 1924, **1**, 181.
35. Ritchie, W. T.: Auricular Flutter, Green, Edinburgh, 1914.
36. Ritchie, W. T.: Complete Heart Block with Dissociation of the Action of the Auricles and Ventricles, *Proc. Log. Soc. of Edinburgh*, 1905, **25**, 1085.
37. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exp. Med.*, 1913, **17**, 429.
38. Robinson, G. C., and Draper, G.: Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart. I. The Effect of Mechanical Stimulation of the Vagus Nerve, *J. Exp. Med.*, 1911, **14**, 217.
39. Rothberger, C. J., and Winterberg, H.: Ueber Vorhofflimmern und Vorhofflattern, *Arch. f. d. ges. Physiol.*, 1914, **160**, 42.
40. Schott, E.: Ueber Ventricelstillstand (Adams-Stokes Anfälle) nebst Bemerkungen ueber andersartige Arrhythmien passagerer Natur, *Deutsch. Arch. f. klin. Med.*, 1920, **131**, 211.
41. Semerau, M.: Ueber Rückbildung der Arrhythmia Perpetua, *Deutsch. Arch. f. klin. Med.*, 1918, **126**, 161.
42. Smith, F. M.: Further Observation on the T-wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, *Arch. Int. Med.*, 1920, **25**, 673.
43. Strauss, D. S., and Hamburger, W. W.: The Significance of Cardiac Irregularities in Reference to the Operability of Cases of Cholecystitis and Duodenal Ulcer, *J. Am. Med. Assn.*, 1924, **82**, 706.
44. Sutherland, G. A.: Auricular Flutter in Acute Rheumatic Carditis, *Proc. Roy. Soc. Med.*, 1914, **7**, 133.
45. Vinnis, E. W. G.: Dissociation la plus complete entre le rythme ventriculaire et le rythme auriculaire, *Nederl. Maandschrift v. Geneesk.*, Lege, 1920.
46. Wedd, A. M.: Clinical Auricular Flutter, *Ann. Int. Med.*, 1924, **3**, 69.
47. Willius, F. A., and Barnes, A. R.: Myocardial Infarction, *J. Lab. and Clin. Med.*, 1925, **10**, 427.
48. Willius, F. A.: Auricular Flutter with Established Complete Heart Block, *Am. Heart J.*, 1926-1927, **2**, 449.
49. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropin, *Arch. Int. Med.*, 1915, **16**, 989.
50. Wilson, F. N.: Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, *Heart*, 1924, **11**, 61.
51. Wiltshire, H.: A Case of Heart Block Illustrating the Behavior of the Auricle During Periods of Prolonged Ventricular Silence, *Heart*, 1923, **10**, 201.
52. Wolferth, C. C.: Intermittent Impure Auricular Flutter with Special Reference to Onsets and Offsets of Paroxysms and the Effects of Vagal Stimulation, *Arch. Int. Med.*, 1925, **35**, 42.

"RESTING INFECTION" IN VARICOSE VEINS: ITS DIAGNOSIS AND TREATMENT.

BY G. DE TAKATS, M.D., M.S., F.A.C.S.,

ASSISTANT PROFESSOR OF SURGERY AT NORTHWESTERN UNIVERSITY MEDICAL SCHOOL;
ADJUNCT STAFF, WESLEY MEMORIAL HOSPITAL, CHICAGO, ILL.

(From the Department of Surgery, Northwestern University Medical School.)

VARICOSE veins are frequently infected. The flow of blood is greatly retarded in the dilated veins, and is reversed in the standing position. Bacteria circulating in the blood stream may easily

localize in the wall of such veins. Acute attacks of phlebitis have been observed following removal of teeth or tonsils, thus demonstrating the importance of foci in the production of phlebitis.

A physician had recurrent attacks of thrombophlebitis in varicose veins. When some abscessed teeth were pulled, an acute phlebitis developed in the veins of both lower extremities, which had been in a quiescent stage for some time. A similar flareup has been observed following tonsillectomies in 3 cases. In 1 case an old deep thrombophlebitis became activated, a thrombus broke loose and resulted in a fatal pulmonary embolism.

Another group of patients with phlebitis give the history of an acute respiratory infection, following which a thrombosis occurred in the previously existing venous dilatations. That typhoid fever and influenza are frequently followed by an iliac thrombosis, is well known. Less attention has been called to the fact that the "common cold" in patients suffering from varicose veins may start up an acute superficial phlebitis.

A young lady, aged 24 years, had some varicose veins of the hereditary type for 6 years. They were never inflamed. During an acute cold, for which she went to bed for 3 days, an acute thrombophlebitis developed in the varicose veins, with a massive periphlebitic exudate.

A third group of infections in superficial veins originates in the chronic varicose ulcer, which is a source of ascending infection in veins and perivenous lymph channels. This chronic infection results in a definite local immunity of the tissues, a condition that will be discussed a little later.

Finally there is a group of patients, in whom no detectable source of infection is evident, and who develop "out of a clear sky" a massive thrombophlebitis. This "spontaneous" thrombophlebitis may be precipitated by a slight injury, by lifting a heavy weight or other mild trauma, but sometimes even such a history is absent. Some patients, who have had varicose veins for many years, will undergo an operation or childbirth and will develop a thrombophlebitis during convalescence. That this is not solely due to the slowing of the blood flow and possible changes in the coagulability of the blood, is demonstrated by a rise in pulse, leukocyte count and temperature, accompanying the thrombophlebitis. Occasionally of course an aseptic thrombosis occurs, but this is very rare in my experience.

In a group of 31 cases of acute phlebitis in varicose veins, 6 could be traced in all probability to teeth and tonsils, 5 followed acute respiratory infections, 3 were precipitated following an operation, 1 a fracture of the clavicle, and in 16 no definite source of infection could be elicited. None were found in the presence of varicose ulcers.

It must be emphasized that we are dealing here only with phlebitides in the varicose vein, and that infections in the normal super-

ficial veins or in the deep veins are not included in these figures and constitute a somewhat different problem.

The importance of infection in varicose veins is obvious. It constitutes the most important contraindication to the injection treatment of varicose veins. It is not my object in this paper to discuss the treatment of the acute, manifest phlebitis in the varicose vein. Obviously no one would think of treating such veins with injections. Of far greater significance, however, is the type of vein which harbors bacteria but at examination does not show any obvious clinical evidence of infection. It has seemed to me that of all the discomfort and untoward results that may follow the injection treatment, the activation of a slumbering infection is the most frequent and the least emphasized. It is the object of this paper to define "resting infection" in varicose veins, its recognition and possible treatment.

Resting Infection in the Tissues. Pathogenic bacteria may exist for a long time in the tissues without showing any clinical evidence of activity. A real truce is formed between bacteria and the tissues. Particularly the reconstructive surgery following the World War encountered such hidden infections around foreign bodies or in bone and joint infections. Men of great surgical experience, such as Kuttner, Lexer, and Melchior, had the embarrassing experience of lighting up such resting infections many years after the original injury or infection took place. It was particularly Payr's Clinic in Leipzig, however, which emphasized the importance of recognizing resting infection before orthopedic operations, particularly when mobilizing joints.

In an article of fundamental importance, Payr¹ evolved a systematic examination of previously infected bones and joints. He believed that particularly streptococci, gas and tetanus bacilli are most apt to persist in a resting stage, from which the surgical trauma may awake them to full virulence.

Bacteriologic literature has only recently become interested in "resting" bacteria. According to Kendall,² resting bacteria were first discussed by Guastel. Dr. Arthur J. Kendall defines "resting" bacteria as "bacteria fully endowed with their potentialities, but constrained from multiplying by withholding of nutritives, conducive to their growth." When bacteria are taken at the height of their growth from suitable media, washed free from the culture and are vigorously aerated, they do not multiply after that, but show certain metabolic activities which Dr. Kendall has investigated in great detail.³

The "resting infection" in the tissues and the "resting bacteria" in the test tube may not be identical phenomena. The resting bacteria are deprived of their media completely. The resting infection in the tissues is well encapsulated by fibrous tissue but is not entirely deprived of circulation. This is best illustrated by the fact

that foreign protein injections may result in focal reactions in these encapsulated areas. It is also probable that local immune bodies are formed against such bacteria which are thus held in check. Such immune reactions are of course not operating *in vitro*. Nevertheless, the study of the resting bacteria *in vitro* must prove to the clinician that bacteria exist for a long time in a potentially active state, without multiplying.

Resting Infection in Varicose Veins. The source of infection in varicose veins has been discussed above. In the course of ambulatory ligations, which I have advocated for certain types of varicose veins,⁴ sections of the saphenous veins were placed in suitable media and studied by the methods of Dr. Kendall in his research laboratory. A report on the obtained cultures will be made by Drs. Kendall and Jacques. Of the 58 cultures made up to the time of the present writing over one-half were positive and not due to contaminations. It must be remembered that these veins were ligated in the absence of any clinical infection, so that we are really dealing with a resting infection. The bacteria also seemed to grow very slowly and the cultures were frequently negative up to a week or 10 days, indicating the sluggish response of these hibernating organisms.

The Activation of Resting Infection by the Injection Treatment. It seems certain, then, that a large percentage of varicose veins harbor resting infection. This is significant from the standpoint of treatment. Of a little over 1500 patients treated in the Varicose Vein Clinic of Northwestern University and in my own private and consulting practice, 23 cases of acute phlebitis have been seen following injection treatment. These cases were all massive thrombophlebitides, extending from the site of injection up to the groin, with a marked periphlebitic edema, and often a rise in temperature.

The first of these cases was seen 4 years ago in consultation with a physician, who had made 2 injections of 50 per cent dextrose into a varicose vein below the knee. Three days later when I saw him, the patient had a temperature of 101° F. and a massive thrombophlebitis extending from the site of injection as high as Poupart's ligament. A large painful mass of periphlebitis was present just below Poupart's ligament. The clot must have extended to the saphenofemoral junction.

The patient did not give a history of previous phlebitis. I did not recognize at that time that we were dealing with an activation of a resting infection, and a thorough bacteriologic study was made of the rest of the injected solution, which, however, gave negative results. Since then my associates and I have observed enough cases to convince us of a typical syndrome: an acute thrombophlebitis, patchy or massive in character, as a result of an activated resting infection. There may or may not be a history of previous phlebitis. At the time of injections, there is no gross evidence of inflammatory reaction in the veins. From 2 to 7 days following the injections the

patient returns complaining of great pain, and often, though not always, a rise in temperature is present. The injected vein and also a large segment above it is thrombosed with a large periphlebitic exudate around it. The skin is red and hot. Frequently if the valves are insufficient the clot extends to the saphenofemoral junction.

I do not advise prolonged immobilization for these cases. The temperature drops in a few days, the patients are allowed to get up. The legs are strapped from the toes to a point which lies beyond the upper limit of the clot. We have not lost one such case through embolism. In analyzing the cases of fatal embolism following injection treatment one always finds two factors present: (1) An acute phlebitis following the injections; (2) a prolonged rest in bed. The embolism then is due to a soft infected thrombus, not an aseptic irritative thrombus, and the favoring influence of prolonged immobilization as an additional factor.

If one could avoid the injection into veins harboring resting infection, the most significant reaction could be eliminated.

The Recognition of Resting Infection in Varicose Veins. The following points have proved to be of value in the diagnosis of resting infection:

1. *The History of Previous Phlebitis.* Some patients, if thoroughly questioned will tell of hard painful patches along the course of the vein. Curiously enough, patients who have gone through an acute attack of phlebitis do not show marked reactions following vein ligation or injections. I have injected such patients from 2 to 3 months after acute symptoms subsided, very cautiously, with small amounts of the blandest irritant, namely, 50 per cent dextrose solution. No acute phlebitis developed in such cases. Nevertheless, the history of a preceding phlebitis should make one suspicious of a possible flareup, and methods of recognizing latent infection, to be described later, should be employed.

2. *The Presence of a Varicose Ulcer.* Of 195 cases of varicose ulcer, which have been treated by injections and Unna's casts, not 1 patient developed an acute phlebitis. Of course, acutely inflamed ulcers were first treated with casts alone, until the acute symptoms subsided. The absence of an acute flareup in this and the preceding group strongly suggests the development of a local immunity of the veins to the preceding infection.

3. *The Presence of an Acute Respiratory Infection During Injection Treatment.* One patient injected during an acute cold by a physician developed an acute superficial phlebitis. This case strongly emphasizes the importance of postponing the treatment during acute infections, but does not belong to the conception of a resting infection.

4. *Clinical Signs and Symptoms of Resting Infection.* The patients who developed an acute phlebitis following injections, did not have a history of acute phlebitis, or if so, it dated several years

back. There were no varicose ulcers. On inspection such veins do not show any obvious inflammatory reaction, such as hyperemia or edema, but sometimes a residual pigmentation, owing to a hemorrhagic exudate. On palpation, particularly after emptying the veins of the blood, the walls are thickened, painful on pressure and small phleboliths may be palpable. The most important finding is a rise in skin temperature above such veins, which can well be detected by palpating with the palm or surface of the hand and exactly determined by measurements with a skin thermometer. The following table gives a few measurements of skin temperature in suspected resting infection. (Table 1.) It can be seen that a difference of 3° to 4° C. is not uncommon. In order to ascertain that no venous stagnation *per se* is responsible for the rise in temperature, the readings were not made above dilated veins. While the skin thermometer may not always be available, the palm of the hand readily recognizes differences of more than one-half of a degree. Hence this important sign can always be elicited.

There are no systemic changes in these slumbering infections. Temperature and leukocyte count are normal. Payr reported that around resting infections occasionally a local leukocytosis was found. In a few determinations, there was no appreciable difference between white counts from the ear and around the infected vein. Much more fruitful seemed certain provocative measures, which served to produce a mild activation of the resting infection. After numerous trials, three procedures proved harmless and useful. The puncture of the vein, without any injection, is the mildest possible trauma and yet in 1 patient who had a marked rise in local temperature, a simple puncture was enough to produce a marked patch of thrombophlebitis, complete occlusion of the vein and a painful infiltration which lasted for weeks. The administration of diathermy for 5 minutes over the suspected area, has given a marked rise in skin temperature the next day. Naturally the other leg is also treated for control. In 1 patient the skin temperature rose from 34.8° to 40.2° C. 24 hours after 5 minutes of diathermy. The control leg became 2 degrees warmer. A 30 to 40 per cent skin erythema dose of Roentgen ray (125 to 135 R units) with heavy filters applied to the questionable area and to a symmetrical area on the other leg will be followed by a rise in skin temperature, best recorded 4 hours after irradiation in ambulatory patients. The idea of producing acute symptoms in chronic infections by Roentgen ray has been proposed by Fründ⁵ and elaborated upon by Maske⁶, but has not been applied in this connection to my knowledge. Chart I shows temperature readings before and several hours after such provocative irradiation in suspected cases of resting infection. For practical purposes, one 4-hour reading seems sufficient.

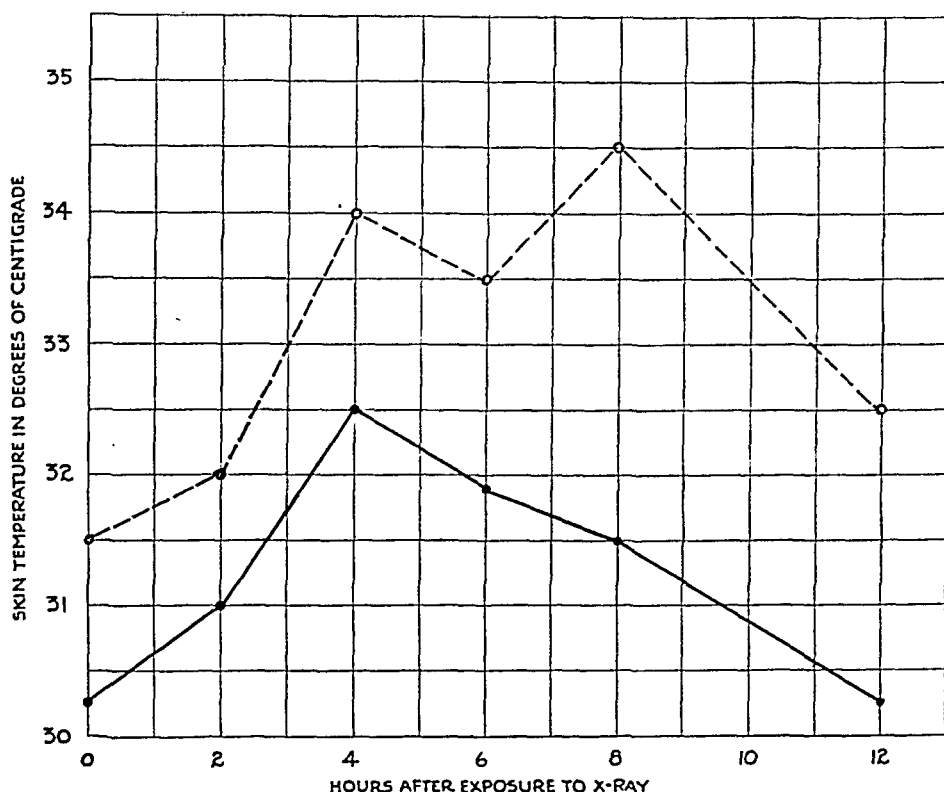
When the wall of the vein reacts with obvious signs of inflammation to mechanical, thermic or physical stimuli, it is to be expected

that the injection of an irritant may produce a sudden, violent thrombophlebitis, which is a most important untoward reaction of injection treatment. If then the history of the patient, or the local findings, particularly the rise in skin temperature suggest a resting

TABLE I.—SKIN TEMPERATURES IN SUSPECTED RESTING INFECTION.

Patient.	Clinical diagnosis.	Control side.*	Affected side.	Difference
W. B. Cl.	Postphlebitic edema with comp. circulation	31.8	34	2.2
D. L. Cl.	Varicose veins; no history of infection	30	34.6	4.6
I. Fa.	Subacute sup. phlebitis	30.2	34.8	4.6
N. M.	Atypical dilations; 6 months pregnant	31.8	36	4.2
G. Mca.	Atypical veins, possibly old deep thrombosis	29.4	34.4	5
I. R.	Recurrent attacks of deep phlebitis—last attack 6 weeks ago . .	32.4	34.2	1.8

* Skin temperatures are expressed in centigrade and were measured with a Tycos skin thermometer.



Skin temperature following an exposure to Roentgen rays; 125 R was given with 2 mm. aluminum filter on the affected side and the same dose on the control side. Temperatures were taken with a Tycos skin thermometer in the same room. Room temperature was 27° C. Straight line = temperature of control side; interrupted line = temperature of limb with resting infection. This patient, aged 46 years, had recurrent attacks of deep phlebitis. The last attack was 6 weeks previous to examination. Note that the temperature difference between the sides was only 1.2° C. before irradiation.

infection, one of the provocative measures, preferably Roentgen ray should be applied. A negative response still does not exclude a resting infection, but a positive result is an important danger signal. It contraindicates injection treatment.

The Treatment of Resting Infection in Varicose Veins. When the above provocative measures have made a diagnosis of resting infection, first a careful search for obvious foci, such as teeth and tonsils must be made. The removal of such foci may aggravate the latent phlebitis, but this is quite infrequent and only temporary. It is more difficult to eliminate pelvic infections, infected thrombi in pelvic veins, which follow childbirth or miscarriages and continuously reinfect the veins of the lower extremities. One such case has been observed for a long time. Every change of weather, every slight exertion would light up small periphlebitic patches, but at the same time the thrombosed veins in the broad ligament became painful to the touch. It is almost impossible to clear up these infections.

Repeated doses of Roentgen ray for the resistant resting infections, with supportive casts of gelatin-glycerin, injections of own blood or mild foreign protein therapy offer possibilities which must be investigated. In 3 cases which showed marked provocation at first, it was possible to clear up the residual infection, so that 3 months later injections could be given without any reaction. Whether these patients became desensitized or had actually no more resting infection could only be decided by immunologic studies. Dietrich⁷ was able to produce an increased reaction of the vascular endothelium by intravenous sensitization with dead colon bacilli but also with nonspecific protein.

Comment. The recognition and treatment of resting infection in varicose veins is of great practical importance. My associates and I have treated up to date over 1500 patients with injections. The occurrence of sloughs has been emphasized in the literature, but very little has been said about the acute phlebitides, which must occur, according to experience in consultations, in a high percentage of cases. It usually takes the physician unawares. A systematic search for resting infection, first applied to joints and bones by Payr and adopted here for varicose veins, will eliminate a small but definite number of patients in whom treatment is better postponed. The idea of a time limit, after which operations can be safely performed following suppurations, is no safeguard. Kilbourne⁸ has given a clear presentation of the difficulties encountered with patients who have a history of phlebitis. The activation of a deep phlebitis is of course far more serious than that of a superficial one. Delater⁹ and Kilbourne do not reject all cases which have a history of deep phlebitis, and I fully agree with them. But more important than time limit, age of the patient, or site of the original infection (superficial or deep) is the recognition of resting infection. When

the deep veins are affected the superficial veins seem to be equally infected or perhaps sensitized. Infection may be harbored in the tissues for years. That a repair of a ventral hernia following a drained appendiceal abscess may be followed by renewed suppuration even after a year has been permitted to elapse, has been personally observed. Tetanus bacilli may be encapsulated around foreign bodies for 8 years and have produced a fatal tetanus infection. Testing for resting infection in contractures of the hand before reconstruction operations would be very well worth while. With the exceptions of varicose veins, test massage could be used in other areas of the body as a provocative measure. I did not think it safe to massage veins with resting infection for fear of mobilizing mural thrombi; but in joints and old contractures it could be employed as a good stimulus for activating infection.

Summary. 1. Varicose veins are frequently infected. The source of infection lies in teeth, tonsils, and pelvic infections, acute respiratory infections or in varicose ulcers. Phlebitis in a varicose vein is a definite contraindication to injection treatment.

2. In a group of cases, the infection subsided to a point where there are no clinical signs of inflammation. Nevertheless the trauma of injection treatment may activate the resting infection in the veins. Resting infection in other tissues, particularly in bones and joints has received attention in the literature. It is characterized by the presence of pathogenic bacteria in the tissues which do not show any clinical evidence of activity. Such bacteria have been cultivated from varicose veins and are now being studied by Kendall.

3. The acute thrombophlebitis as a result of a resting infection activated by the injection treatment is a typical picture. These patients should have proper support and may get up as soon as the rise in temperature subsides. They do not need prolonged immobilization like a deep phlebitis. The author believes that they are safer if treated ambulatory.

4. The recognition of resting infection would eliminate a number of untoward inflammatory reactions following injection treatment. The presence of a varicose ulcer does not seem to bring about such reactions during treatment, as if a local immunity had developed. The history of a previous phlebitis should force one to look for local symptoms. Tender, thickened veins, palpable phleboliths, but particularly a rise in surface temperature should suggest resting infection.

5. To activate such resting infection, provocative measures, such as vein puncture, diathermy, Roentgen ray may be employed. The obtained reaction is measured in 4 hours by the rise in skin temperature, preferably with a skin thermometer.

6. When resting infection is diagnosed, injections should not be undertaken at that time. Obvious foci of infection should be eliminated. Repeated small doses of Roentgen ray, mild protein

therapy, together with adequate support of the limb may clear up the residual infection. Three months later the provocative tests may become negative, at which time the injection treatment is permissible. The infection, however, may not clear up for years, particularly if the site of infection is in the pelvis.

BIBLIOGRAPHY.

1. Payr, E.: Ueber Erkennung und Behandlung der ruhenden Infektion, *Arch. f. klin. Chir.*, 1928, 153, 515.
2. Kendall, A. I., Friedemann, T. E., and Ishikawa, M.: Studies in Bacterial Metabolism, *J. Infec. Dis.*, 1930, 47, 186.
3. Kendall, A. I., and Ishikawa, M.: Significance of Certain Reactions Induced by "Resting" Bacteria, *J. Infec. Dis.*, 1929, 44, 282.
4. de Takats, G.: Ambulatory Ligation of the Saphenous Vein, *J. Am. Med. Assn.*, 1930, 94, 1194.
5. Fründ, H.: Unsere Erfahrungen mit der Röntgenbehandlung chirurgischer Tuberkulosen, *Beitr. z. klin. Chir.*, 1913, 87, 208.
6. Maske, B.: Ergebnisse der Untersuchung auf ruhende Infektion an Extremitäten, *Arch. f. klin. Chir.*, 1931, 164, 58.
7. Deitrich, A., and Schröder, K.: Abstimmung des Gefäßendothels als Grundlage der Thrombenbildung, *Virch. Arch. f. path. Anat. u. Physiol.*, 1930, 274, 425.
8. Kilbourne, N. J.: Varicose Veins: Indications and Contraindications to Injections, *Ann. Surg.*, 1931, 93, 691.
9. Delater, G., and Chailly, M.: Phlebite ancienne et fibrose curative des varices, *Presse méd.*, 1931, 39, 95.

THE GENETIC ORIGIN OF TUMORS SUPPORTED BY THEIR SIMULTANEOUS AND SYMMETRICAL OCCURRENCE IN HOMOLOGOUS TWINS.

BY JOSEPH MCFARLAND, M.D., Sc.D.,

AND

T. STANLEY MEADE, B.S., M.D.,

PHILADELPHIA.

(From the McManes Laboratory of Pathology, University of Pennsylvania.)

It is customary to look upon tumors as new growths that appear because cells are disturbed and stimulated to growth by chronic irritation. That certain tumors may arise in this manner is not improbable, and there is good experimental evidence of their so doing, but that all tumors, or even the greater number, can thus be accounted for seems to us improbable.

The facts brought out by Slye's studies of cancer inheritance in mice and the discovery of "cancer families" have made us suspect that the origin of most tumors is to be found in the constitution of the sufferers and traced to a genetic source. We hope that the facts brought together in this paper may be of some assistance in settling the question—are human tumors hereditary?

Heredity is the greatest determining factor in life. With the exception of such accidents as traumatism, infection and intoxica-

tion, almost everything that happens in the course of an individual's life, from the commencement of his embryonal development to his last gasp in old age seems to be determined by his inheritance and foreshadowed in his germ plasm. The anatomic structure, the physiologic functions, the nervous and psychic reactions and the social behavior of every individual are above everything else the results of his inheritance.

The most painstaking observation of an individual tells us nothing about his heredity. That one man is tall, another short; one slender, another stout; one light in complexion and freckling in the sun, another dark and tanning uniformly; one light-hearted and careless, another stern and stingy; one with a tumor, another without—is a matter of every-day observation and usually occasions no comment because it is expected that people will so differ. But the study of many individuals soon shows that they fall into groups, that there are families and races of tall people, short people, dark people, fair people, and that it is inheritance that has given to each the qualities described. Characters or qualities that are regularly inherited and make us what we are we regard as normal and belonging to the species; those that we have not been accustomed to see in our ancestors appear to be new and are regarded as pathologic.

Variation is the general tendency of all living things—no two of the same kind are exactly alike—and Darwin thought them to be of supreme importance in the evolution of species. But later biologists, following de Vries, have come to the conclusion that “mutation” is probably more important.

The cause of mutation or suddenly appearing striking variation is unknown. It, or something comparable to it, may occasionally modify the germ plasm in such manner as to result in congenital deformity, insanity, dyscrasia, metabolic disturbance or tumor. Once changed by mutation the germ plasm may carry the newly acquired character through many generations, or may end it with one generation, when it results in a state incompatible with the propagation of its abnormal kind.

The persisting new character, no matter how vicious, descends through generation after generation, sometimes appearing, sometimes failing to appear accordingly as its genes are concentrated through the matings of those having it, or diluted through the matings of those that do with those that do not have it. Much human germ plasm now contains abnormal genes tending to feeble-mindedness, color blindness, tone deafness, epilepsy, insanity, polydactylism and tumors.

Some genetic characters stand in relation to one another as opposites, for example, light color to dark color, and in matings behave as hybrids, their appearance, disappearance and final separation in subsequent generations taking place according to Mendel's formula.

In general, one quality or character takes precedence over the other, appears and is called *dominant*, while the other that may not appear is called *recessive*. Dark color is, for example, almost always dominant over light, and gives all hybrid light and dark animals a dark color. But when such hybrids are mated together the invisible light color invariably sooner or later makes its appearance in the offspring, some of which will be light, some dark, some still hybrid. Those not acquainted with these facts are often surprised to find two dark animals giving rise to a family of both light and dark offspring. It is the invisible recessive abnormal characters contained in the germ plasm of many human beings that occasion the unexpected appearance of the malformed or otherwise abnormal children by which so many families are distressed.

Twins have been studied from many points of view, and readers interested will find much valuable information in the papers by Abt,² Ahlfeld,^{3,4} Ansiaux,⁵ Galton,⁴² Kleinwächter,⁵⁸ Lange,⁵⁹ Leven,^{63,64} Meirowsky,⁶⁹ Meirowsky and Leven,⁷⁰ Murray,⁷⁸ Newman,⁸¹ Siegl,⁹⁶ Siemens,^{98,99} Wilder^{117,118} and Wimberger.¹²⁰

Twins are of two kinds, which we shall speak of as *heterologous* and *homologous*. In the former and more frequent each individual arises from its own separate egg fertilized by its own separate spermatozoön. In this way not only may there be twins, but triplets, quadruplets, quintuplets or sextuplets. Each is an individual in itself, having no more to do with its fellow or fellows than with other brothers and sisters: *all that they have in common is the accident of simultaneous gestation.*

Such twins may be of different sexes or of the same sex; they are rarely strikingly alike in appearance, they may differ in complexion, in disposition and in every other way, and one may be deformed or defective, the other normal. Because of their different origin and makeup they are variously called heterologous, di-zygotic, bi-ovular, di-chorionic, dissimilar or nonidentical twins. Three-fourths of the twins born are of this dissimilar kind, and in our present discussion they play no part.

The remaining fourth of the twins are homologous and are the accidentally double products of a single egg fertilized by a single spermatozoön.

The fertilized egg is composed of germ plasm that determines how the developing individual shall be formed, how he shall look, how his parts shall interact, what he shall eat, how he shall behave and perhaps what maladies he may suffer from and of what and how he shall die.

It begins its development by dividing into two cells of equal size; these again divide into 2, so that there are 4, then 8, then 16, then 32 and so on. The cells resulting from the earliest divisions, the primary blastomeres, are equivalent and toti-potent, so that, should they become separated, each is capable of producing an entire creature exactly like that into which the entire egg should have

developed. If the blastomeres be separated at a slightly later stage of development, when there are many instead of 2 cells, the result may be the same if the material is equally divided and completely separated. But the longer the separation is postponed, the more difficult it becomes, the cells tending to cling together. With partial separation, conjoined twins or double monsters are formed. A double monster is 1 individual partly divided into 2, and homologous twins 1 individual entirely divided into 2. Such twins are called homologous, en-zygotic, uniovular, monochorial, similar or identical. It is such twins that are of interest in connection with this paper.

In the first division of the ovum each half receives as nearly as the vicissitudes of mitosis will permit exactly the same quantity of of all the genetic materials and influences, so that if separated the 2 blastomeres develop along exactly the same lines: they look alike and behave alike. As sex is determined in the egg, these double creatures being from the same egg, are always of the same sex. It is commonly stated that they are *identical*, and in the days when Weismann's ideas of the "invariability of the germ plasm" were popular it was supposed that they could not vary in the least particular. This was a mistake. They can never be identical because in the multitudinous cellular mitoses involved in development and growth the amount and quality of chromosomal substance entering into the dividing cells is never precisely the same.

To prove that an exact correspondence in homologous twins is not to be expected it is only necessary to examine such photographs of conjoined twins, that is, those whose bodies were not completely separated in the blastomere stages, as appear in Gould and Pyle's.⁴⁹ "Anomalies and Curiosities of Medicine," where there are portraits of the Siamese twins, the Orissa sisters (Radica-Doddica) and the Blazek sisters, in all of whom the faces are sufficiently unlike to enable the individuals easily to be told apart. Even more interesting is the case of a monster with two heads, two thoraces, four arms, one pelvis and two legs, the Tocci brothers, whose two faces are quite different.

If the twins were really identical, as was once thought upon theoretical grounds, every quality, peculiarity or defect in one would have to be exactly repeated in the other. For reasons just pointed out, there may be many small matters in which there is no exact correspondence, though there are never any great differences between them. Small scattered lesions (freckles and moles) occur in homologous twins without symmetry, but larger *nævi*, both cellular and vascular, are usually identical and symmetrical. Good papers upon this subject are by Bardach,⁷ Meirowsky and Leven⁷¹ and Siemens.¹⁰¹

In considering symmetry in the distribution of the peculiarities and defects shared by twins it must be remembered that it sometimes appears in a reversed form. The right and left hands of every

normal person are symmetrical in that they are in almost perfect correspondence in every particular except that the thumb of one is on the right and that of the other on the left, and so on for the fingers. This is spoken of as "mirror symmetry," and the abnormalities of homologous twins sometimes occur in this form. Thus, the aortæ may both arch to the left which is usual, or both arch to the right, which is a variety of situs inversus viscerum, or one may arch to the left, and the other to the right—mirror image, or symmetry.

The complete anatomic correspondences obtaining between abnormal homologous twins is perhaps nowhere better shown than by a hermaphroditic pair studied by Vrölik (*Over dubbilde misgebornten*, Amsterdam, 1840). Each was marred by encephalocele occipitale con hernia cerebri, hare lip, cleft palate, 6 digits on each extremity, double cryptorchia, scrotal fissure, imperforate urethra, permeable urachus opening at the umbilicus, bicornate uterus and partial inversion of the abdominal viscera.

It is inconceivable that anything except equal division of the germinal influences could bring about such complete correspondence between 2 defective individuals.

From a careful study of the cases recorded in the literature, the following generalization seem to be justified, *heterologous twins never suffer from identical malformations*, nor does one of homologous twins ever suffer from malformation not shared by its fellow.

If interest in twins were new one might question whether data gathered from the literature might not lead into error rather than the truth. For example, if one of twins is malformed or diseased the matter appears ordinary and no record is made of it, but if both be similarly disturbed the interesting coincidence (!) may attract sufficient attention to be published. We do not believe, however, such an error to be probable. The normal and pathologic correspondences between homologous twins have been matters of interest since Galton wrote his *Hereditary Genius*, in 1871, and the collecting and reporting of cases have increased with each subsequent decade without the number of correspondences being offset by exceptions.

In some cases the homology of twins remains a matter of doubt, especially when, though of the same sex and complexion, they do not resemble one another as strikingly as usual. The absolute criterion is a single placenta common to both. But in many cases interest in the homology or heterology of the twins is deferred until it is no longer possible to learn anything about the placenta. It is then necessary to have recourse to a totality of large and small resemblances. Siemens⁹⁸ deduces the uniovular nature of the twins through the correspondence of external characteristics: sex; color of the eyes and skin; form and color of the hair; distribution of freckles; distribution of congenital anomalies of the skin vessels, such as telangiectases, cutis marmorata and acroasphyxia; keratoses and folliculitis; grooves of the tongue; tooth form and distribution;

shape of head, face, ear, hands and nails; general body form; psychic characteristics; congenital anomalies and diseases; dactyloscopy; capillary microscopy and eye refraction. When all these agree there can be little doubt about the monozygous or uniovular nature of the twins.

Homologous twins are similar in disposition and tastes, no doubt because of their identity of structure and function. If the psychic activities are disturbed in one, corresponding disturbances usually show in the other. Considerable literature upon psychic disturbances common to both of homologous twins was found in our studies, but as our interests did not center about the nervous and mental disturbances, we made no attempt to collect all of the published cases, nor did we determine whether there are any recorded cases in which one of the homologous twins suffered from one of these maladies independently of the other. The matter being of interest in connection with the general theme of our study, it seems well to mention it, and the same is true of a few miscellaneous constitutional, *i. e.*, physiologic and metabolic, peculiarities. They turned up unexpectedly, were noted in our bibliography, but were not further pursued.

TABLE 1.—PSYCHIC ABNORMALITIES USUALLY COMMON TO BOTH OF HOMOLOGOUS TWINS.

Amentia—Gordon.⁴⁸
 Dementia precox—Campbell,²⁰ Frantz,⁴⁰ Gordon,⁴⁸ Johnson,⁵⁵ Lange,⁶⁰ Parker,⁸² Sukanoff.¹⁰⁶
 Epilepsy—Toledo.¹⁰⁸
 Depressive insanity with persecutory delusions—Gordon.⁴⁸
 Feeble-mindedness—Campbell,²⁰ Wilson.¹¹⁹
 Friedrich's ataxia—Hess.⁵³
 Hallucinatory states—Gordon.⁴⁸
 Hypochondriasis and delusional insanity—Richmond.⁸⁹
 Mania—Bradley,¹⁵ Campbell,²⁰ Gordon.⁴⁸
 Melancholia—Campbell,²⁰ Gordon,⁴⁸ Mickle.⁷²
 Paranoia—Campbell,²⁰ Gordon.⁴⁸
 Psychosis—Gill.⁴⁶

Psychic Abnormalities Sometimes Common to Both of Seeming Homologous Twins, Sometimes Affecting Only One of Them.

Mongolian idiocy—Abt,² Gautier and Coeytaux,⁴⁴ Halbertsma,⁵¹ MacLean,⁶⁷ Mitchell and Downing,⁷⁴ Murray,⁷⁸ Petzoldt,⁸⁵ Ruben and Klein,⁹¹ Strauch.¹⁰⁵

Special Sensory Peculiarities Shared by Both of Homologous Twins.

Hearing—Identical peculiarities—MacFarlan.⁶⁶
 Sight—Night blindness—Danforth.³²

Physiological and Constitutional Peculiarities Common to Both of Homologous Twins.

Abnormal susceptibility to atropin—Siegl.⁹⁶
 Albinism—Garrod.⁴³
 Asthma and rheumatic ophthalmia—Cockayne.²⁴
 Congenital lymphangiectatic edema—Maslowski.⁶⁸
 Diabetes—Bunce and Dougherty,¹⁸ Curtis,³⁰ Twinem,¹⁰⁹ Wilson.¹¹⁹
 Goiter—Ansiaux,⁵ Petschacher,⁸⁴ Siemens.⁹⁷

Petzoldt,⁸⁵ who has made a careful study of Mongolian idiocy, was able to collect 35 pairs of twins, in 1 or both of which the disease appeared. Her chief difficulty seems to have been to establish the homology of the twins when of the same sex and when the appearance of one was as changed as the occurrence of Mongolian idiocy, implies. Among her cases were 14 pairs of twins of different sex, of course, *heterologous twins, among which more than 1 child was never affected*. But there were 21 pairs of twins of the same sex, some of which may have been heterologous, some homologous. Among them 1 child was affected 15 times, and both affected 6 times. It is, of course, quite possible that the only homologous twins were the 6 pairs in which both children were simultaneously and similarly affected, and as of the total 35 pairs, only one-fourth (9) should be homologous, the findings seem to be in favor of the genetic character of the idiocy.

The 2 cases of MacFarlan⁶⁶ and Danforth³² were the only ones dealing with similar disturbances of the special senses that we unearthed, but others may have been reported. We made no special search for them.

That homologous twins suffer similarly from cutaneous disorders may mean that some of the diseases are of genetic origin, that the twins possess identical susceptibility and resistance, they they were exposed to the same contagion or that they were fed upon the same diet according to the nature of the disease. A great number of cases are recorded by Siemens.⁹⁷

The regularity with which the great majority of the congenital anatomic defects were found to be common to both of homologous twins and peculiar to one of heterologous twins was so pronounced and interested us so greatly that we made an earnest endeavor to collect every case that may have been reported.

If the reader had any doubt as to the genetic origin of the psychic, sensory, cutaneous and metabolic correspondences of homologous twins this long list of anatomical malformations common to both twins should satisfy him of its probability. Coincidence as an explanation seems to be entirely out of the question. If there are not entirely too many cases and entirely too broad an anatomic distribution to make it possible, all that is necessary is to note that with the exception of the little group of congenital hydroceles, cryptorchism and hernias *no cases are recorded in which one of these conditions affected only one of the homologous twins, and that no such coincidences are reported among heterologous twins*.

We do not insist that all physical and other defects shared by homologous twins are necessarily germinal; there must be exceptions and there are, no doubt, coincidences. For example, in the Confederate Museum, at Richmond, Va., there is a photograph of L. T. and H. J. Walker, twin confederate soldiers, sitting side by side, each having lost his left leg as the result of battle wounds.

TABLE 2.—ANATOMIC MALFORMATIONS COMMON TO BOTH HOMOLOGOUS OR UNIOVULAR TWINS.

- Cardiac—Patent ductus arteriosus—Smith.¹⁰⁴
- Cranial—Dolicocephalia—Miller⁷³ observed it in 4 pairs of twins.
- Encephalocele—Lehman.⁶²
- Hydrocephalia—Abt,² Riviére and Drouin.⁹⁰
- Microcephalia—Whitney¹¹⁶ observed it in 4 pairs of twins.
- Dental—Abnormal dentures and identical caries—Weitz.^{112,113}
- Erupted incisors at birth—Balard.⁶
- Deficient teeth—Ahlfeld,^{3,4} Wimberger.¹²⁰
- Excessive teeth—Ahlfeld.⁴
- Full sets of teeth at birth—Ahlfeld,^{3,4} in a double monster.
- Identical abnormal spacing of the teeth—Weitz.^{112,113}
- Facial—Hare lip—Davis.³⁴
- Rhinocephaly—Ellis.³⁸
- Gastric—Congenital hypertrophic pyloric stenosis—Bilderbach,¹¹ Cockayne and Sheldon,²⁵ Davis,³⁵ Moore.⁷⁷
- Genital—Absence of external genitalia—Abelin.¹
- Hypospadias—Lehman,⁶² Rumpel.⁹²
- Phimosi—Miller.⁷³
- Pseudohermaphroditism—Abt,² von Mons,⁷⁵ Naegele,⁷⁹ Petschacher,⁸⁴ Saviard, cited by Bullock,¹⁷ Curling.²⁹
- Intestinal—Congenital megacolon—Popper.⁸⁷
- Lingual—Short lingual frenulæ—Miller⁷³ observed in 2 pairs of twins.
- Mammary—Polymastia—Siemens,⁹⁷ Weitz.^{112,113}
- Ophthalmic—Amyotrophia congenita—Forbus and Wolf.³⁹
- Complete bilateral ophthalmoplegia, Vossius (cited without reference by various writers).
- Congenital nuclear ophthalmoplegia—Wilson.¹¹⁹
- Convergent strabismus—Bunce and Dougherty,¹⁸ Waardenburg.^{110,111}
- Palatal—Cleft palate—Brophy,¹⁶ Davis,³⁴ Shearer (see Brophy).
- Renal—Polycystic disease—Abelin.¹
- Skeletal—Club foot—Abelin,¹ Berkheiser,¹⁰ Smilga.¹⁰³
- Congenital dislocation of the hips—Hale,³² Whitney.¹¹⁶
- Depressed sternum—Miller⁷³ observed this in 2 pairs of twins.
- Osteogenesis imperfecta—Waltz and Lieberman.¹¹⁵
- Parietal osseous defect—Cohn,²⁶ Nesensohn.⁸⁰
- Polydactylism and digital deformities—Danforth,³³ von Siebold.⁹⁴
- Pelvis reversus—Corey.²⁷
- Spina bifida—Abt,² d'Outrepont.³⁷
- Somatic—Nanism—Goldstein and Schenck.⁴⁷
- Umbilical—Hernia—Abelin.¹
- Hypertrophy—Miller⁷³ observed it in 5 pairs of twins.
- Anatomical Malformations Occurring Sometimes in Only One of Homologous Twins, Presumably Examples of Mirrored Symmetry; Sometimes in Both.*
- Dextrocardia—Debreuil and Chambardel,³⁶ Monteiro,⁷⁶ Pezzi and Carugati,⁸⁶ Smith.¹⁰⁴
- Situs inversus viscerum—Miller,⁷³ Reinhardt.⁸⁸
- Anatomical Malformations Apparently Accidentally Associated in Twins.*
- Cryptorchism and congenital inguinal hernia—Abelin,¹ Birkenfeld.¹² The latter author collected 7 cases of hernia in homologous twins and 6 in heterologous twins; also 4 cases of cryptorchism in the former and 4 in the latter.
- Congenital dislocation of the crystalline lens—Whitney.¹¹⁶
- Double congenital hydrocele—Riviére and Drouin.⁹⁰
- Incarcerated right scrotal hernia—Schafer.⁹³

No one would think of incriminating the germ plasm in this interesting coincidence.

We now come to the subject of prime importance: How does the matter stand with respect to tumors?

When a child is born with a deformity or with some physiologic deficiency as deafmutism or color blindness, or when in later life it develops diabetes or leukemia, the general tendency has been, and in most places still is, to view the circumstances as a newly acquired and individual matter. When one individual is found to have a tumor it also is looked upon as a mere circumstance in the life of the individual. But if the simultaneous symmetrical occurrence of congenital anatomic defects or physiologic deficiencies in each of homologous twins can be assumed to prove the genetic origin of those abnormalities, shall the similar simultaneous and symmetrical occurrence of tumors in homologous twins be ascribed to some other cause? Would it not increase the probability that such matched tumors are no mere vagaries of the individual somaplasm acted upon by internal and external stimuli but that they are fixed characters predetermined in the egg and as inescapable as other germinal influences?

In white mice the inheritance of cancer susceptibility admits of little doubt; it not only determines that the mouse shall have a cancer, but also where its cancer shall be situated. The same may eventually be found to be true of man. Although an effort has recently been made to show by mathematic calculation, based upon the law of probabilities, that the number of apparent cases of cancer inheritance is no greater than the number of possible coincidences, the coincidence theory scarcely seems a likely one when, as in the family studied by the senior author, a father and 3 sons all are found to suffer from carcinoma of the colon, these 4 being among 10 cases of malignant disease in three generations of a not very large family.

If a surgeon be consulted by a young man with sarcoma of the testis he usually inquires about antecedent injury, and when the patient remembers that some months before he met with an accident involving the diseased part he looks upon it as an accident and his conviction that tumors result from injury grows. If shortly afterward he sees another patient similarly affected who, however, cannot recollect ever having been injured in anyway he may continue his original belief and make a note that as the tumors are said sometimes to follow a very slight injury the patient has probably forgotten all about it. But what will he think should he next be consulted by twin brothers each of whom has sarcoma of the left testis. neither ever having been injured so as to notice it? Probably he will call it a curious and interesting coincidence. But if he shortly learns of another pair of twins with exactly similar tumors, will he still accept the coincidence theory? Will he not be likely to seek

for some other explanation? Such cases as these are to be found in this interesting literature.

The already referred to small differences that obtain between homologous twins permit a limited variation in the localization and appearance of their corresponding tumors, but in general they are of the same kind, at about the same place, and make their appearance at about the same time. They may, therefore, be said to be *similar*, *symmetrical* and *simultaneous*.

To read about the similar, symmetrical and simultaneous tumors of homologous twins is extremely interesting, but a far deeper impression of their importance and conviction of their meaning follows the examination of Burkhard's¹⁹ photograph, in which the twins, 2 middle-aged women, with the clothing removed from the upper part of their bodies, sit side by side, appearing almost exactly alike, each with a visible tumor in the upper outer quadrant of the left breast.

TABLE 3.—TUMORS OCCURRING SIMULTANEOUSLY AND SYMMETRICALLY IN EACH OF HOMOLOGOUS TWINS.

Arranged according to their localization—

Bones—Chondrous exostoses—Birkenfeld,¹³ Gould.⁵⁰
 Brain—Cerebellum—Medulloblastoma—Leavitt.⁶¹
 Cerebrum—Glioma—Joughlin.⁵⁶
 Breasts—Adenofibroma—Burkhard.¹⁹
 Carcinoma—Burkhard.¹⁹
 Eye—Melanoma—Silcock.¹⁰²
 Retinoblastoma—Benedict.⁹
 Kidney—Congenital cystic tumors—Abelin.¹
 Larynx—Papillomas—Szontagh.¹⁰⁷
 Ovary—Carcinoma—Kimbrough.⁵⁷
 Cystoma—Twinem.¹⁰⁹
 Skin—Nævi—Bardach,⁷ Gesell,⁴⁵ Hutchinson,⁵¹ MacFarlan.⁶⁶
 Testis—Sarcoma—Champlin,²¹ Wells.¹¹⁴
 Uterus—Myoma and adenocarcinoma—Croom.²⁸
 Adenocarcinoma—Weitz.¹¹²

TABLE 4.—TUMORS OCCURRING SIMULTANEOUSLY AND SYMMETRICALLY IN EACH OF HOMOLOGOUS TWINS.

Arranged according to the type and disposition of the tumors—

Benign—Adenofibroma of the breast—Burkhard.¹⁹
 Ecchondrosis—Birkenfeld,¹³ Gould.⁵⁰
 Cystoma of the kidney—Abelin.¹
 Cystoma of the ovary—Twinem.¹⁰⁹
 Nævi—Bardach,⁷ Gesell,⁴⁵ Hutchinson,⁵¹ MacFarlan.⁶⁶
 Papilloma—Szontagh.¹⁰⁷
 Malignant—Carcinoma of the breast—Burkhard.¹⁹
 Carcinoma of the ovary—Kimbrough.⁵⁷
 Carcinoma of the uterus—Croom,²⁸ Weitz.¹¹²
 Glioma (medulloblastoma of the brain)—Leavitt,⁶¹ Joughlin.⁵⁶
 Melanoma of the eye—Silcock.¹⁰² There is some doubt about this case.
 Retinoblastoma of the eye—Benedict.⁹
 Sarcoma of the testis—Champlin,²¹ Wells.¹¹⁴

Leukemia and Hodgkin's disease, both of which are of unknown cause and nature, the former sometimes appearing to be inherited and shown by Slye to be intimately associated with cancer inheritance in mice, the latter regarded by Medlar as a primary malignancy of the bone marrow, have also been reported as simultaneously affecting homologous twins:

Chronic lymphatic leukemia—Dameshek, Savitz and Arbor,³¹ Siegel.⁹⁵
Hodgkin's disease—Peacock.⁸³

That it should be possible thus to bring together tumors of a dozen different kinds simultaneously and symmetrically affecting a dozen different parts of the bodies of homologous twins is remarkable, especially when one learns that there seems to be no reported case in which one homologous twin suffered from a tumor without its fellow being similarly affected.

Cancer is one of the most frequent and most important tumors, but usually does not make its appearance until the second half of life. Twin cancer observations, therefore, require that both twins shall have lived long enough to develop the disease and shall have lived near enough together for each to know about the other, and for each to be studied in comparison with the other by the same observer. Notwithstanding these obstacles, cancers of the breast, uterus and ovaries of twins are to be found in our lists.

The evidence points strongly in the direction of a genetic determination for the tumors of twins. And if for the tumors of twins, why not for tumors in general? Does not each year see additions to the list of tumors assigned to congenital defects?

Concerning the nature of the tumor predisposition these studies have little to say. To consider it as a constitutional predisposition or a widespread tissue susceptibility is to meet the difficulty of accounting for the symmetry of the lesions. A general predisposition might, indeed, lead to the occurrence of tumors in each of the twins, but would it explain their identical localization? It seems as though there must be an anatomic focus at which the disturbance has its beginning—perhaps some Cohnheimian residual embryonal cellular tissue.

Conclusions. 1. Genetic influences existing in the egg dominate the physical development, physiologic function, psychic activity and intellectual behavior of every individual.

2. When the genetic influences are imperfect, developmental, vegetative, functional and psychic abnormalities result.

3. Since homologous twins arise from a single egg and consist of approximately equal quantities of material normally destined to produce a single individual but which through some circumstance of early separation has been made to produce two, they closely resemble one another in every particular.

4. The similar, simultaneous and symmetrical occurrence of abnormalities in both of homologous twins tends to prove the genetic origin of those abnormalities.

5. Tumors occurring in homologous twins seem always to be similar, symmetrical and simultaneous.

6. This seems to be strong evidence of the genetic origin of such tumors.

7. If tumors are of genetic origin in twins they may be of the same origin in others.

8. We feel, therefore, that tumor occurrence in general may not be a matter of accident but one that is determined in the germ plasm.

BIBLIOGRAPHY.

1. Abelin, C.: Spiegelmissbildungen bei Zwillingen, Zentralbl. f. Gynäk., 1928, 52, 249.
2. Abt, I. A.: Diseases and Fate of Twins, J. Iowa State Med. Soc., 1924, 14, 395.
3. Ahlfeld, J. F.: Die Misbildungen des Menschen, etc., Leipzig, 1880-1882.
4. Ahlfeld, F.: Beitrag zur Lehre von den Zwillingen, Arch. f. Gynäk., 1876, 9, 196.
5. Ansiaux: Die Lehre von den Zwillingen, Prague, 1871; cited by Kleinwächter (not available for reference).
6. Balard, P.: Eruption precoce de deux dents de lait chez deux jumelles, Gaz. hebdom. d. sc. méd. de Bordeaux, 1923, 44, 270.
7. Bardach, M.: Aystematisierte Naevusbildungen bei einem eineiigen Zwillingsspaar, Ztschr. f. Kinderheilk., 1925, 39, 542.
8. Bauer, J., Krebs and Vererbung: Wien. klin. Wchnschr., 1931, 44, 129.
9. Benedict, W. L.: Retinoblastoma in Homologous Eyes of Identical Twins, Arch. Ophth., 1929, 2, 545.
10. Berkheiser, E. J.: Unilateral Congenital Talipes in Twins, J. Am. Med. Assn., 1926, 87, 1300.
11. Bilderbach, J. D.: Hypertrophic Pyloric Stenosis in Homologous Twins, Northwest. Med., 1928, 27, 182.
12. Birkenfeld, W.: Cryptorchism and Inguinal Hernia in Uniovular Twins, Deutsch. med. Wchnschr., 1929, 55, 1043.
13. Birkenfeld, W.: Zur Erbllichkeit der multiplen kartilaginaren Exostosen, Deutsch. Ztschr. f. Chir., 1930, 226, 397.
14. Birkenfeld, W.: Uniovular Twins with Cleft Palate, Lip, Jaw, etc., Beiträge z. klin. Chir., 1927, 141, 257.
15. Bradley, J. A.: Manic Depressive Psychosis in Identical Twins, Am. J. Psychiat., 1930, 9, 1061.
16. Brophy, T. W.: Cleft Lip and Palate, Philadelphia, P. Blakiston's Son & Co., 1923, p. 90.
17. Bullock: Treasury of Human Inheritance, College of Physicians, 1909, 3, 50.
18. Bunce, A. H., and Dougherty, M. S.: Diabetes Mellitus in Twins, J. Am. Med. Assn., 1929, 92, 53.
19. Burkhard, H.: Gleichzeitige und gleichartige Geschwulstbildung in der linken Brustdrüse bei Zwillingsschwestern, Deutsch. Ztschr. f. Chir., 1922, 169, 166.
20. Campbell, D.: Zwillingsirresein und induziertes Irresein, Inaug. Dissert., Leipzig, 1922.
21. Champlin, W. H.: Similar Tumors in the Testes of Identical Twins, J. Am. Med. Assn., 1930, 95, 96.
22. Clark, T. J., and Stibbens, F. H.: Skin Diseases in Twins, California and West. Med., 1926, 24, 777.
23. Cockayne, E. A.: Heredity in Relation to Cancer, The Cancer Rev., 1927, 2, 344.
24. Cockayne, E. A.: Diseases in Homologous Twins, Brit. J. Dis. Child., 1911, 8, 487.
25. Cockayne, E. A., and Sheldon: Hypertrophic Pyloric Stenosis in Uniovular Twins, Proc. Roy. Soc. Med., Sect. on Diseases of Children, 1927-1928, 21, 60.

26. Cohn, M.: Die vererbaren Verknocherungsdefekte der Scheitelbeine, *Med. Klin.*, 1924, 20, 857.
27. Corey, L.: A Singular Case of Malformation in the Human Species, *Med. and Surg. Rep.*, 1868, 18, 316.
28. Croom, Sir John H.: Adenocarcinomas of Uterus in Twins, *J. Obst. and Gynec. Brit. Emp.*, 1912, 21, 330.
29. Curling, T. B.: Cases of Malformation of the Female Sexual Organs, *Med. Times and Gaz.*, 1852, 4, 84.
30. Curtis, W. S.: Diabetes in Twins, *J. Am. Med. Assn.*, 1929, 92, 952.
31. Dameshek, W., Savitz, H. A., and Arbor, B.: Chronic Lymphatic Leukemia in Twin Brothers Aged Fifty-six Years, *J. Am. Med. Assn.*, 1929, 92, 1348.
32. Danforth, C. H.: Resemblances and Differences in Twins, *J. Heredit.*, 1919, 10, 399.
33. Danforth, C. H.: Polydactylism in Negro Twins, *Am. J. Phys. Anthrop.*, 1919, 2, 147.
34. Davis, A. D.: Tripartite Cleft-palate and Double Hare-lip in Identical Twins, *Surg., Gynec. and Obst.*, 1922, 35, 586.
35. Davis, H. A.: Congenital Hypertrophic Pyloric Stenosis in Twins, *J. Am. Med. Assn.*, 1924, 83, 686.
36. Debreuil and Chamardel: Twins and Cardiac Disturbances, *Presse méd.*, 1927, 35, 1157.
37. d'Outrepoint: Beobachtungen und Bemerkungen, *Gemeins. deutsch. Ztschr. f. Geburtsh.*, 1929, 4, 561.
38. Ellis, R.: On a Rare Form of Monstrosity (Twins with Rhinocephaly), *Trans. Obst. Soc. London*, 1866, 7, 160.
39. Forbus, W. D., and Wolf, F. S.: Amyotrophia Congenita in Identical Twins, *Bull. Johns Hopkins Hosp.*, 1930, 47, 309.
40. Frantz, M. H.: Dementia Praecox in Twins, *J. Ment. and Nerv. Dis.*, 1919, 50, 324.
41. Galton, Sir Francis: *Inquiries into the Human Faculty*, New York, Macmillan Company, 1883.
42. Galton, Sir Francis: *Hereditary Genius*, New York, D. Appleton & Co., 1871.
43. Garrod, Sir A.: *Inborn Errors of Metabolism*, London, 1923.
44. Gautier, P., and Coeytaux, P.: Un cas de mongolism chez des jumeaux, *Arch. de med. des enfants*, 1926, 39, 459.
45. Gesell, A.: Mental and Physical Correspondence in Twins, *Scient. Month.*, 1922, 14, 305.
46. Gill, C.: Psychoses in Twins, *J. Ment. Sci.*, 1883, 28, 539.
47. Goldstein, H., and Schenck, M.: An Unusual Case of Dwarfism in Twins, *New York Med. J.*, 1920, 3, 98.
48. Gordon, A.: Psychoses in Twins, *Virginia Med. Month.*, 1925, 52, 181.
49. Gould, G. M., and Pyle, W. L.: *Anomalies and Curiosities of Medicine*, Philadelphia, W. B. Saunders Company, 1897, p. 887.
50. Gould, P.: In discussion of Sir John Hutchinson, *Med. Times and Gaz.*, London, 1880, 2, 578.
51. Halbertsma, T.: Mongolism in One of Twins, etc., *Am. J. Dis. Child.*, 1923, 25, 350.
52. Hale, K.: Congenital Dislocation of the Hips in Identical Twins, *Ann. Surg.*, 1926, 83, 682.
53. Hess, J. H.: Friedreich's Ataxia in Twin Boys, *Med. Clin. North America*, 1922, 6, 1749.
54. Hutchinson, J.: Twins, etc., *Arch. Surg.*, London, 1896, 7, 290.
55. Johnson, D. A.: Dementia Praecox in Twins, *J. Nerv. and Ment. Dis.*, 1925, 62, 41.
56. Joughlin, J. L.: Glioma of Cerebrum in Identical Twins, *Arch. Neurol. and Psychiat.*, 1928, 19, 948.
57. Kimbrough, R.: Coincident Carcinoma of the Ovary in Twin Girls, presentation to Philadelphia Obstetrical Society, November 1, 1928.
58. Kleinwächter, L.: *Die Lehre von den Zwillingen*, Prague, Fhaerpfer, 1871, 6, 246.
59. Lange, J.: Factors of Inheritance and Environment in the Study of Twins, *Ztschr. f. Kinderheilk.*, 1929, 34, 377; 37, 626.
60. Lange, J.: Rôle of Heredity in Pathogenesis of Schizophrenia Observations on Uniovular Twins, *Wien. klin. Wchnschr.*, 1929, 42, 1247.

61. Leavitt, F. H.: Cerebellar Tumors Occurring in Identical Twins, *Arch. Neurol. and Psychiat.*, 1928, **19**, 617.
62. Lehman, L.: Hernia cerebri bij voldrazene levend geborene tweelingen, *Nederl. tijdschr. v. geneesk.*, 1857, **1**, 97.
63. Leven, S. R.: Die Leistungsfähigkeit der zwillingspathologischen Arbeitsmethoden für die aetiologische Forschung, München. med. Wehnschr., 1924, **71**, 404.
64. Leven, S. R.: Eineiigkeit der Zwillinge, *Klin. Wehnschr.*, 1927, **6**, 998.
65. Ludwig, E.: Ueber die Verteilung der Erbmasse unter eineiige Zwillinge, *Schweitz. med. Wehnschr.*, 1927, **57**, 1041.
66. MacFarlan, D.: Identical Hearing in Identical Twins, *Laryngoscope*, 1927, **37**, 846.
67. MacLean, S.: Mongolian Idiocy in One of Twins, *J. Am. Med. Assn.*, 1922, **78**, 13.
68. Maslowski, H.: Zwillinge mit Oedema lymphangiectaticum, *Monatschr. f. Kinderheilk.*, 1928, **40**, 436.
69. Meirowsky, E.: Erblichkeit bei eineiigen Zwillingen und Aetiologie der Muttermale, *Virchow's Arch. f. path. Anat. u. Phys.*, 1927, **266**, 313.
70. Meirowsky, E., and Leven, S. R.: Tierzeichnung, Menschenscheckung und Systematisierung der Muttermale, *Arch. f. Dermat. u. Syph.*, 1921, **134**, 1.
71. Meirowsky, E., and Leven, S. R.: Ueber einem Fall von Riesennaevus nebst Bemerkungen über die Aetiologie der Muttermale, *Arch. f. Dermat. u. Syph.*, 1923, **143**, 272.
72. Mickle, A. F.: Melancholia in Twins, *J. Ment. Sci.*, London, 1884, **30**, 67.
73. Miller, N.: Ueber homologe Zwillinge, *Jahrb. f. Kinderheilk.*, 1893, **36**, 333.
74. Mitchell, R. G., and Downing, H. F.: Mongolian Idiocy in Twins, *Am. J. Med. Sci.*, 1926, **172**, 866.
75. von Mons: Twins with Hermaphroditis Masculinus, *J. d. Bruxelles*, 1808, **47**, 467.
76. Monteiro: Aorta Crossed to Right in Identical Twins, *Arq. de anat.*, Lisbon, 1929-1930, **13**, 245 (not available for reference).
77. Moore, H. L.: Twins with Hypertrophic Pyloric Stenosis, *South. Med. J.*, 1924, **17**, 187.
78. Murray, G. R.: Twins in Health and Disease, *Lancet*, 1925, **1**, 529.
79. Naegele, D. F. C.: Beschreibung eines Falls von Zwitterbildung bei einem Zwillingsspar, *Deutsch. Arch. f. d. Physiol. (Meckel's Arch.)*, 1819, **5**, 136.
80. Nesensohn: Inaug. Diss., Tübingen, 1857.
81. Newman, H. H.: Physiology of Twinning, Hull Zoölogical Laboratory, Univ. of Chicago Press, 1923.
82. Parker, G. H.: Dementia Praecox in Identical Twins, *J. Nerv. and Ment. Dis.*, 1926, **63**, 135.
83. Peacock, C.: Communication, *Lancet*, 1904, **2**, 1517.
84. Petschacher, L.: Demonstration eineiiger Fälle von endokrinen Funktionsstörung, *Wien. klin. Wehnschr.*, 1922, **35**, 749.
85. Petzoldt, G.: Mongolismus bei einem von Zwillingen, *Monatschr. f. Kinderheilk.*, 1930, **47**, 174.
86. Pezzi and Carugati: Twins and Cardiac Disturbance, *Cuore e circolazioni*, 1924, **8**, 361 (not available for reference).
87. Popper, J.: Congenital Megacolon, *New York Med. J.*, 1920, **113**, 1030.
88. Reinhardt: Ein Fall von Situs viscerum inversus totalis bei Zwillingen, *Deutsch. milit. Ztschr.*, 1912, **41**, 931.
89. Richmond, W.: Psychic Resemblances in Identical Twins, *Am. J. Psychiat.*, 1926, **6**, 161.
90. Riviere M., and Drouin: Double hydrocephale dan une grosseuse geméllaire, *Gaz. hebdomadaire de sci. méd.*, 1910, **4**, 342.
91. Ruben, M. S., and Klein, S.: Mongolian Idiocy in Both of Twins, *Arch. Pediat.*, 1926, **43**, 552.
92. Rumpel: Ueber identische Misbildungen, besonders Hypospadie, bei eineiigen Zwillingen, etc., *Frankf. Ztschr. f. Path.*, 1921, **25**, 53.
93. Shafer, F. W.: Personal Communication to the senior author.
94. von Siebold, E. C.: Bericht über die in der Königl. Entbindungsanstalt für Göttingen vorgefallenen Ereignisse, *Neue Ztschr. f. Geburtsh.*, 1843, **13**, 243.
95. Siegel, A. E.: Lymphatic Leukemia Occurring in Twins, *Atlantic Med. J.*, 1928, **31**, 748.
96. Siegl, J.: Ein Beitrag zur Zwillingspathologie (Susceptibility to Atropin Shared by Homologous Twins), *Arch. f. Kinderheilk.*, 1926, **78**, 198.

97. Siemens, H. W.: Die Zwillingspathologie, Berlin, 1924.
98. Siemens, H. W.: Das Problem der Erbgleichheit bei der eineiigen Zwillingen, Virchow's Arch. f. path. Anat. u. Phys., 1927, 263, 666.
99. Siemens, H. W.: Lässt sich die keimplasmatische Naevustheorie aufrechterhalten? Arch. f. Dermat. u. Syph., 1924-1925, 148, 625.
100. Siemens, H. W.: Zwillingspathologischen Untersuchungen der Mundhöhle, Arch. f. Dermat. u. Syph., 1924, 147, 409.
101. Siemens, H. W.: Eine Ergebnisse Zwillingspathologischen Forschung auf dem Gebiete der Hautkrankheiten, Klin. Wchnschr., 1924, 3, 309.
102. Silcock, A. Q.: Hereditary Sarcoma of Eyeball in Three Generations, Brit. Med. J., 1892, 1, 1079.
103. Smilga, G.: Zur Frage der Klumpfussbildung bei Zwillingen, München. Wchnschr., 1928, 75, 177.
104. Smith, K. S.: Congenital Cardiac Disease in Identical Twins (Patent ductus arteriosus), Arch. Dis. Child., 1929, 4, 330.
105. Strauch, A.: Mongolian Idiocy in Both Twins, J. Am. Med. Assn., 1923, 81, 2181.
106. Sukanoff, S.: Insanity in Twins, Ann. Med. Psychol., 1900, 12, 214.
107. Szontagh: Ueber Dispositionen, Berlin, 1918.
108. Toledo, R. M.: Notes on Two Cases of Epilepsy in Twins, J. Ment. Sci., 1919, 65, 262.
109. Twinem, F. P.: Identical Twins and Heredity, New York State J. Med., 1927, 27, 1192.
110. Waardenburg, R. J.: Course of Strabismus and Amblyopia in Twins, Klin. Wchnschr., 1927, 6, 603.
111. Waardenburg, R. J.: Course of Strabismus and Amblyopia in Twins, Nederl. Tijdschr. v. Geneesk., 1928, 72, 5783.
112. Weitz, Prof. Wilhelm: Studien an eineiigen Zwillingen, Ztschr. f. klin. Med., 1924, 101, 115.
113. Weitz, Prof. Wilhelm: Ueber die Bedeutung der Erbmasse für das Gebiss nach Untersuchungen bei eineiigen Zwillingen, Deutsch. Monatschr. f. Zahnheilk., 1924, 42, 89.
114. Wells, H. G.: Personal Communication to Twinem.¹⁰⁹
115. Wetz, W. E., and Lieberman, B. L.: Report of a Case of Osteogenesis Imperfecta in Twins, Am. J. Obst. and Gynec., 1927, 14, 49.
116. Whitney, E. A.: Microcephaly in Twins, Med. J. and Rec., 1929, 130, 158.
117. Wilder, H. H.: Physical Identity of Duplicate Twins, Science, 1928, 27, 451.
118. Wilder, H. H.: Duplicate Twins and Double Monsters, Am. J. Anat., 1904, 3, 387.
119. Wilson, S. A. K.: Organic Nervous Diseases in Identical Twins, Arch. Neurol. and Psychiat., 1929, 21, 477.
120. Wimberger, H.: Eineiige Zwillinge, Ztschr. f. Kinderheilk., 1921, 31, 216.

FOOD POISONING DUE TO A YELLOW MICROCOCCUS FROM MILK.

By F. W. TANNER, Ph.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF ILLINOIS,

AND

R. J. RAMSEY, M.S.,

ASSISTANT IN DAIRY MANUFACTURES, UNIVERSITY OF ILLINOIS, URBANA, ILL.

(From the Department of Bacteriology, University of Illinois.)

RECENT investigations in the field of food poisoning have given more satisfactory evidence for opinions and conclusions which were formerly based largely on assumption or circumstantial evidence.

Discovery of the formation of agents poisonous by mouth by bacteria not hitherto connected with food poisoning has given investigations in this field new impetus.

While studying the cause of malt flavor in raw milk, one of us (R. J. R.) became ill with a severe gastroenteritis. He was prostrate for 2 days with severe symptoms of food poisoning, which included cramps in abdominal regions, weakness of legs, violent diarrhea, and loss of appetite. The food in this case was revealed to be raw milk which had been inoculated with a pure culture of a yellow micrococcus isolated from a sample of normal raw milk delivered to a commercial milk plant. It was not suspected that this organism was harmful, because of its common occurrence in raw milk delivered to the milk plant. It was being studied as the cause of undesirable flavors; however, a number of observations presented below, as well as a search of the literature, convinced us that the organism in question was responsible for the gastroenteritis and quite similar if not identical with others described in the literature.

While the literature on this subject is not voluminous, it is quite convincing. Barber⁴ reported a white micrococcus from milk which caused many attacks of gastroenteritis. It was found in the udder of a cow which, as far as could be determined, was normal. Guests staying overnight at the farm where the milk of this cow was used without pasteurization were often made seriously ill with symptoms of typical food poisoning. Barber himself was so affected several times.

The cases showed a curious seasonal incidence, occurring only during the hot dry season of the year. It was also noticed that none of these attacks occurred following the ingestion of fresh milk or cream. Fresh milk was harmless, and the toxin was evident only after the milk had stood for several hours at room temperature. Kittens, puppies and monkeys showed no noticeable symptoms after ingesting pure cultures of the organism. Human volunteers, however, were seriously affected after ingesting such cultures.

Results of another series of observations on food poisoning caused by a member of the Coccaceæ have been published recently by Dack, Cary, Woolpert and Wiggers³, Dack, Jordan and Woolpert¹ and Jordan.² In the first report, Dack and his colleagues described an outbreak of food poisoning caused by a layer sponge cake with so-called cream filling. Among the three types of bacteria which were isolated was a yellow hemolytic staphylococcus, veal-infusion-broth filtrates of which proved to be toxic when administered to rabbits intravenously. Human volunteers who drank different amounts of the filtrates became ill with definite symptoms of food poisoning. The organism was destroyed by exposure to 80° C., for 15 minutes. Heating at 100° C., for 30 minutes did not render the filtrates innocuous. These data suggested to Jordan² the examination of other staphylococcus strains for formation of products causing

food poisoning when ingested. With the aid of human volunteers he tested six strains of diverse origin. Formation of a substance which produced gastrointestinal disturbance was demonstrated. Activity of the substance was destroyed by boiling and was either destroyed or greatly weakened by being heated at from 60° to 65° C., for 30 minutes. Dack, Jordan and Woolpert¹ tried to immunize men and rabbits with the toxic agent. Their results were negative. It is interesting to note that Jordan's data on the effect of heat on the toxic factor do not agree with those reported by Dack and his colleagues. The toxic agents of the strain used by the latter investigators seem to have been more heat resistant.

Experimental. The organism reported in this paper was isolated from milk which had undergone a change in flavor. This flavor, known in the dairy industry as "malt" flavor, is probably due to various bacteria, one of which may be the organism here discussed. It is a micrococcus isolated from the udder of a cow which, as far as could be determined, was perfectly normal. A preliminary report on the organism was published by Ramsey and Tracy.⁶

The microscopic appearance of this organism is subject to considerable variation. It differs from the more saprophytic types in size, shape and especially arrangement. The latter are usually larger, more regular in appearance, and occur usually in irregular masses. Our organism, however, is quite small and shows ability to take different arrangements. When first isolated, it does not form the usual irregular masses, but occurs principally in pairs or short chains of 5 or 6 units. This tendency is gradually lost if the organism is grown on solid media, but may again be restored by cultivation in liquid media. Comparison with a culture of the organism supplied by Dr. Dack revealed no differences in characteristics. We prefer to refer to our organism⁸ as a micrococcus, in keeping with the suggestions of Hucker (1928).

Because of its extreme variability in pigment production, it is somewhat difficult to classify. In the present study involving 104 cultures, much difficulty was experienced in drawing a boundary line between the orange, yellow, and the white types. Cultures which were white when first isolated often produced pigment after repeated transfers on plain agar. On the other hand, colored cultures frequently lost their ability to produce pigment. However, cultivation on Loeffler's blood serum medium resulted in a marked reduction of variations in pigment production. Cultures which did not produce color on plain agar were again able to produce it after the first transfer to Loeffler's blood serum medium. Our organism is one of the transparent types and produces a yellow-orange pigment on Loeffler's medium. On plain agar it may be practically white.

Considerable pertinent information was inadvertently secured before it was realized that the micrococcus might cause symptoms

of illness. One of us (R. J. R.) as reported above, was made quite ill by drinking raw milk which had been inoculated with the yellow micrococcus.

Another member of the staff of this laboratory also showed typical symptoms of food poisoning after ingestion of a pure culture of the organism used to produce malt or caramel flavor in milk. The symptoms were identical with those reported by Barber and Dack, *et al.* They included dizziness, cramps in the abdomen, general weakness and diarrhea. Acute symptoms persisted for only a day or so. They were followed by a prolonged period of weakness. Before this organism was suspected as the cause of the symptoms about twenty others, members of a group which visited the laboratory, were allowed to taste a sample of milk into which the organism had been inoculated. Several of these men complained of having been made ill with symptoms which have been reported above.

These observations stimulated a study of the organism and its ability to cause food poisoning. Since it had been shown with sufficient satisfaction that the organism would cause illness in human beings, attempts were made to reproduce the symptoms in monkeys and kittens.

Four kittens were fed milk cultures of the organism (culture 127). In less than 1 week, 2 of them were definitely sick. One had severe diarrhea with bloody stools while the other passed considerable mucus. The 2 remaining kittens had persistent diarrheal stools until the inoculated milk was removed from the diet.

When monkeys were used experimentally, there were no noticeable effects of feeding milk cultures, or plain broth filtrates, except in one instance. One monkey to which 20-cc. portions of a 24-hour milk culture of strain 128 were fed 5 times had very thin diarrheal stools. There were no other marked symptoms of food poisoning as far as could be determined. We are inclined to agree with Dack that monkeys may not be suitable for studies of some phases of food poisoning. The most direct method is to use human beings.

Since monkeys failed to show definite symptoms of illness when fed with cultures of micrococci, kittens were again used. Three weeks old kittens were selected. None of these animals had received any other food than their mother's milk. Three kittens were fed 10-cc. portions of a 24-hour milk (sterile) culture of strain 128 for 4 successive days. The kittens were placed in separate cages so that the droppings could be carefully watched. The kittens had been so observed for several days before feeding the culture. After the fourth feeding, all but the control showed symptoms of intestinal disturbance. All had thin, watery stools. One kitten lost its appetite and vomited. Another one had considerable mucus in the stool. The control was perfectly normal.

According to Barber⁴ and Dack³ very little, if any, immunity is acquired when the toxin is taken orally. Barber found that four

previous attacks would not protect him against a fifth one. Dack stated that immunity might be acquired orally in a few cases. The variations in resistance between different human volunteers are very noticeable.

Since his illness, one of us (R.J.R.) has tasted as many as 100 milk cultures in 1 hour with no noticeable effects. The milk was merely held in the mouth for a few seconds, to obtain the flavor, and was not swallowed. Whether or not this tolerance is due to an acquired immunity from continuous tasting of milk cultures or from a lack of a sufficiently large dose is a matter to be determined later. Recent work at the Lister Institute indicates that toxin production by the micrococci is a variable factor. There was some indication that the carbon dioxide and oxygen balance was important in toxin formation. Nontoxic strains of *Staphylococcus aureus* were rendered toxic by changing the carbon dioxide-oxygen balance.

The data reported here seem significant in that they furnish added reasons for carefully controlling milk supplies. Breed⁵ has shown that micrococci are common in fresh milk. To argue that these organisms are unimportant would be a refusal to face the facts. There are still many cities and communities where pasteurized milk is relatively unknown. The quality of most raw milk supplies is very poor in the hot, dry season of the year. The bacterial counts may range anywhere from a few thousand to hundreds of millions per cubic centimeter. Milk is not the only offender, for ice cream made from raw products may also harbor many such organisms. Custard fillings often contain large numbers of similar bacteria. These organisms in milk may also be very important from an infant nutrition standpoint. Many babies and small children are no doubt fed milk which is literally teeming with common micrococci. Symptoms of illness in infants evidenced by vomiting after milk feeding may be due to agents formed by bacteria as well as to protein sensitization.

This important health problem may be solved as follows: (1) By the rejection of milk from abnormal udders; (2) by the inhibition of the growth of the common udder flora. The importance of rejecting milk from abnormal udders is usually underestimated by those not intimately connected with the grading of milk. Dairy farmers in general do not understand that mastitis milk should not be included with the milk from healthy animals. During the past year, a number of dairymen have inquired at the university as to whether or not the milk from cows infected with garget should be delivered to the city dairies.

Experiments in progress have shown that many herds in the corn-belt are suffering from low-grade infections of the udder. The milk from these animals can be readily picked out by the large numbers of leukocytes and micrococci present as well as by the methylene blue test.

The inhibition of the growth of the common udder flora may be accomplished by prompt refrigeration and pasteurization. The organism which is the subject of this discussion is killed by heating in milk at 61.11° C. (142° F.) in 20 minutes. Milk should be cooled to 50° F. or below immediately after milking and kept cold until consumed. The housewife should not allow milk to stand in warm places until practically sour.

Conclusions.—A member of the Coccaceæ from normal milk which produced symptoms of illness in man when ingested has been described. The symptoms were those usually present in severe gastroenteritis. The organism was destroyed by times and temperatures usually used in pasteurization. Kittens developed symptoms of gastroenteritis while monkeys were resistant to the toxic agent.

BIBLIOGRAPHY.

1. Dack, G. M., Jordan, E. O., and Woolpert, O.: Attempts to Immunize Human Volunteers with Staphylococcus Filtrates That Are Toxic to Man When Swallowed, *J. Prevent. Med.*, 1931, 5, 151.
2. Jordan, E. O.: The Production by Staphylococci of a Substance Causing Food Poisoning, *J. Am. Med. Assn.*, 1930, 94, 1648.
3. Dack, G. M., Cary, W. E., Woolpert, O., and Wiggers, H.: An Outbreak of Food Poisoning Proved to be Due to a Yellow Hemolytic Staphylococcus, *J. Prevent. Med.*, 1930, 4, 167.
4. Barber, M. A.: Milk Poisoning Due to a Type of Staphylococcus Albus Occurring in the Udder of a Healthy Cow, *Philippine J. Sci.* 1914, Sec. B, 9, 515.
5. Breed, Alice F.: New York State Agric. Exper. Sta. Tech. Bull., 1928, p. 132.
6. Ramsey, R. J., and Tracy, P. H.: Food Poisoning Probably Caused by Orange Colored Staphylococcus from Udders of Apparently Healthy Cows, *Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 390.
7. Tracy, P. H., and Ramsey, R. J.: Malt Flavor Caused by Micrococci, *J. Dairy Sci.* 1931 (in press).
8. Hucker, G. J.: The Species of the Genus Micrococcus, *Cent. Bakt.*, Pt. 2, 1925, 64, 481.

INTESTINAL OBSTRUCTION CAUSED BY FOOD: REVIEW OF THE LITERATURE AND CASE REPORT.

BY ALBERT H. ELLIOT, M.D.,

ASSOCIATE PHYSICIAN, DEPARTMENT OF INTERNAL MEDICINE, COTTAGE HOSPITAL,
SANTA BARBARA, CALIF.

(From the Department of Internal Medicine, Cottage Hospital.)

INTESTINAL obstruction due to food is not a rare occurrence. A study of the available literature has revealed 39 cases reported since the year 1910, of which the greater number have appeared since 1914, and all but 10 in Germany or Austria. This is apparently traceable to the increased consumption of coarse foods in these countries as a result of the food shortage due to the World War. Only 4 instances have been reported in the United States during this time and, as will be seen later, the diagnosis was not beyond question.

TABLE 1.—ANALYSIS OF 39 CASES OF INTESTINAL OBSTRUCTION CAUSED BY FOOD

Authors.	No. of cases.	Age and sex.	Predisposing factors.	Obstructing material.	Location of obstruction.	Time from ingestion to appearance of symptoms (in hours).	Diagnosis before treatment.	Treatment.	Outcome.	Comment.
Eichorst . .	2	47 ♀ 49 ♂	None None	909 cherry stones 1010 cherry stones	Term. ileum Rectum	Not known Not known	Tumor. asc. colon Correct	Colostomy Manual removal	Died Recov.	Mass felt in R. L. Q. Symps. of chr. obstruc.
Brunzel . .	3	40 ♂ 50 ♂ 68 ♂	None None None	Beans Not known Not known (cucum.?)	Prob. ileum Ileum? Prob. ileum	Not known Not known Not known	Not stated Food ileus Intest. obstruc.	Enterotomy Enemata Laparotomy	Died Recov. Recov.	Aut.—intest. bleeding; phasin? Diag. ? Diag. ?
Pentkert . .	2	8 ♂ 7 ♂	None None	Poppy seeds Poppy seeds, peas, beans	Not known, colon? Prob. ileum and colon	24 Not known	Ac. append. Ac. append.	Enem.; castor oil Cecostomy	Recov. Died	Ingested poppy soup. Aut.—poppy seeds in cecum with perf. of colon.
Fink . . .	4	? ? ? ?	Not stated Not stated Not stated Not stated	Oats Oats Oats Bran	Ileum Ileum Ileum Ileum	Not known Not known Not known Not known	Not stated Not stated Not stated Not stated	Ileostomy Not stated Laparotomy Laparotomy	Died Died Died Recov.	Perf. of ileus in 1 case; no mech. obstruc.; believes "fermentation catarrh" leads to paralytic ileus.
Walther . .	3	22 ♂ 42 ♂ 26 ♂	None None None	"Ammunition" bread? Corn? "Ammunition" bread?	Prob. ileum Prob. ileum Prob. ileum	24 24 Not known	Food ileus Food ileus Food ileus	Enemata Enemata Enemata	Recov. Recov. Recov.	Diag. ? Reflex urin. retention. Reflex urin. retention.
Schöle . .	2	40 ♂ 32 ♂	Not stated Not stated	Bean mass Bean mass	"Upper bowel" "Upper bowel"	14 34	Not stated Not stated	Enterotomy Enterotomy	Recov. Recov.	
Willmoth . .	4	50 ♂ 20 ♂ 13 ♀ 22 ♀	None None None None	Potato lumps Grape residue Grape residue Pop-corn	Not known Not known Not known Not known	Not known Not known 48 Not known	Not stated Not stated Not stated Not stated	Enemata Enemata Enemata Enemata	Recov. Recov. Recov. Recov.	Diag. prob. correct; all had symps. of ac. intest. obstruc. with peritonitis in 2 cases; material recovered in enemata.
Alexander . .	2	40 ♂ 62 ♂	No teeth Prostectomy 2 mo. ago	Fig (whole) Swollen raisin	Term. ileum Jejunum	Not known 1 to 1	Intest. obstruc. Perf. gast. ulcer	Enterotomy Enterotomy	Recov. Died	Had eaten raisin dumpling.

Goebel	1	44 ♂	None	310 cherry seeds	Rectum	Not known	Correct	Manual removal	Recov.	Symps. of chr. obstruct.
Loesel . . .	2	56 ♂ 61 ♂	None None	Bean mass Corn kernels	Term. ileum Asc. colon?	Not known Not known	Ileus, cause? Ileus, cause?	Enterotomy Laparotomy	Recov. Died	Cecum perf.; peritonitis.
Haselhorst . .	2	63 ♀ ? ♂	None None	Swollen fig Peas, fruit lumps	Term. ileum Lower ileum	Approx. 24 Approx. 4	Ileus, cause? Ileus, cause?	Enterotomy Enterotomy	Died ?	
Griffiths . . .	1	44 ♂	None	1 orange	Meckel's divert.	4	Not stated	Died before operation	tion	
Metge . . .	1	57 ♀	None	Peas, potato lumps	Lower ileum	5	Ileus, cause?	Enterotomy	Died	
Chalmers . . .	1	67 ♂	No teeth; intest. ob- struc. 7 yrs. ago	Fig (whole)	Ileum	6	Intest. obstruct.— etiology?	Enterotomy	Recov.	
Wardill . . .	1	66 ♂	None	Potato, wt. 14 gm.	Term. ileum	3	Intest. obstruct.— etiology?	Enterotomy	Recov.	
Leusden . . .	1	65 ♂	None	Gooseberry skins and seeds	Mid. ileum	5	Obstructing Ca of bowel	Laparotomy only	Died	Aut.—ac. perit.; pulm. embolism.
Krecke . . .	1	46 ♀	Enterocnastomosis for stenosis small bowel 5 yrs. ago	Mushroom fiber	Ileum, at anast.	Approx. 24	Ac. append.	Laparotomy only	Recov.	Mass milked into cecum at oper., later passed per rectum.
Ackman . . .	1	7 ♂	None	Cherry skins and seeds	Term. ileum	8	Correct	Enterotomy	Recov.	Cherry stones palp. in bowel before oper.
Krauss . . .	1	16 ♀	None	Mushroom fiber	Term. ileum	Not known	Append. with "ad- hesion ileus"	Bowel resection	Recov.	
Seifert . . .	1	44 ♀	Billroth II for ulcer 5 yrs. ago	Sauerkraut	Term. ileum	Not known	Intest. obstruct. from adhesions	Enterotomy	Recov.	
Krückenberg .	2	? ♀ ? ♀	Tb. stricture ileum Carcinoma of colon	Mushroom fiber Mushroom fiber	Term. ileum Transv. colon	Not known 8 weeks	Not stated Not stated	Not stated Colostomy	? ?	Symps. of chr. obstruct. Symps. of chr. obstruct.
Bär . . .	1	36 ♂	Removal of anemo- plastoma 20 dys. ago	Mushroom fiber	Term. ileum?	240	Malign. chg. of re- tained testicle with chr. ileus	Incis. of swelling at oper. wound	Died	No aut.; metast. Ca bowel wall with perf. suspected.

This paper is concerned with an analysis of these 39 instances in an attempt to elucidate the pathogenesis of this condition and to emphasize its importance. A case is reported of obstruction due to orange pulp, proved by operation and necropsy.

Selection of Cases. The reports were selected for analysis on the basis of clear-cut symptomatology of intestinal obstruction due, in the opinion of the observer, to a food mass. The salient facts in each instance, together with the reference, are presented in the accompanying table. Instances of gastric bezoar and obstructive fecoliths are not included.

The diagnosis of intestinal obstruction due to food was proved by operation or necropsy in 26 instances. Of the remaining 13 in 2 obstructing cherry stones were removed manually from the rectum, with recovery; in 6 the diagnosis was reasonably certain on the basis of recovering the obstructing material by enemata, with subsequent disappearance of symptoms. There remain 5 doubtful cases in which the obstructing material was not recovered, but in which the symptomatology of ileus was definite and the recovery following the use of high enemata and intestinal antispasmodics corroborative.

Predisposing Factors. It might be suspected that intestinal obstruction from food would occur most often in old persons with atonic digestive tracts, or in persons with concomitant intra-abdominal pathology, such as adhesions, strictures, new growths, etc. The age factor, however, is apparently not of great importance. In this series the age of occurrence varied from 8 to 68 years, with the greatest incidence during the fourth and fifth decades. Only 7 of these patients were 60 years of age or older.

Intraabdominal pathology of a contributory nature was noted in only 4 instances. Krükenberg describes 2 cases of "mushroom ileus." In 1 the terminal ileum proximal to an old tuberculous stricture was filled with mushroom fiber. The other had a constricting carcinoma of the colon, behind which a large mass of similar fiber was found. Bär's patient had 20 days previously been operated upon for a spermatoblastoma, which by adhesions had caused a chronic intestinal obstruction. With the sudden onset of ileus a swelling appeared at the site of the operative wound, which on incision, drained a mass of mushroom fiber. It is a question as to whether the mushroom mass did not rather result from obstruction than initiate it. Unfortunately autopsy was not performed. The final instance is that of Krecke, who describes a "mushroom ileus" in a woman upon whom an enteroanastomosis had been performed 5 years previously for a small bowel stenosis. At the second operation an obstructing mass was found at the point of the anastomosis. It was milked through and later discharged by rectum. In the remaining case records studied there was nothing to suggest that the obstruction had been mediated by anything other than a food mass *per se*.

It should not be concluded that coexistent abdominal pathology is not of contributory significance. Although no attempt was made to eliminate those case reports in which other causes for obstruction were present, it is evident that in most of these instances the obstruction would be attributed to the pathologic alteration and not to the food. Hence the case would not be reported in this connection and would not be included in this series. Rather is the conclusion warranted that food may cause obstruction *per se* without the operation of a contributory factor of this nature.

Two other predisposing factors of minor importance should be mentioned. In 4 instances the obstructing food was swallowed without mastication because in 3 a whole fig was recovered; in 1 an entire half orange. It was specifically stated that 3 of these patients were edentulous.

Several observers mentioned the ingestion of a large volume of fluid with vegetable food as possibly causing a swelling of the fibers, resulting in an increase in bulk sufficient to cause intestinal blockage.

Obstructing Material. This was in most instances vegetable or fruit substance with a high content of indigestible residue, such as skins, seeds or fiber. The complete list of foods is as follows:

	Cases.		Cases.
Mushrooms	5	Poppy seeds	2
Cherries (stones)	4	"Ammunition" bread	2
Beans	4	Sauerkraut	1
Figs	3	Gooseberries	1
Oats	3	Raisins	1
Potatoes	2	Half an orange	1
Apple, pear, peas	2	Popcorn	1
Corn	2	Bran	1
Grapes	2		

Most of these foods are common articles of diet, with the exception of poppy seeds which were used to make soup in certain portions of Germany, and of "ammunition" or "war" bread, the composition of which was not given. It was not felt that the poppy seeds liberated enough opium to cause symptoms, but that the disturbance following their ingestion was entirely of mechanical origin.

Appearance Time of Symptoms. The length of time between the ingestion of the obstructing food and the appearance of symptoms was accurately ascertained in 16 instances. It varied from 1 to 240 hours. In the latter case the obstruction was probably in the colon secondary to a new growth, so may be excluded. The average time of onset of symptoms for the remainder was 12.4 hours. In these instances the obstruction was probably without exception in the small bowel.

Location of Obstruction. In those instances where it was accurately determined either at operation or necropsy, the obstruction was usually in the terminal ileum a short distance proximal to the ileocecal valve. The entire small bowel was generally distended, and the serosa of the terminal ileum was deep red to purple in color.

In some instances the bowel in the immediate region of the mass was in a state of spastic contraction. The colon, and particularly the cecum was collapsed. In a number of instances free fluid was present and there was evidence of peritonitis. In 2 cases where the obstructing material was a "pulpy bean mass" the entire intestinal tract was enormously distended by gas. Perforation of the ileum was noted in only 1 instance. Death resulted from peritonitis.

There were 5 cases in which the obstruction was definitely determined to be in the large bowel. One of them, previously mentioned, had an obstructing mass of mushroom fiber in the transverse colon behind a constricting carcinoma. One of Loessl's patients had at operation a distended ascending colon and a perforation of the cecum through which was drained approximately 1 liter of corn kernels. Death resulted. Of the remaining 3, in 2 the rectum was filled by cherry stones. One of these patients had the symptoms of subacute intestinal obstruction; the other, only constipation. The last instance was that of a woman with symptoms of chronic obstruction in whom at operation the terminal ileum, cecum and ascending colon were found to contain 909 cherry stones.

It is evident that in uncomplicated instances the terminal ileum is the site of predilection for obstruction of this nature.

Symptoms. The symptomatology was that of acute intestinal obstruction. The picture presented was modified by the duration of the obstruction at the time the patient was seen and by complicating factors such as peritonitis. Cramping, generalized abdominal pain, nausea, vomiting and constipation were usually mentioned. The outstanding feature of the physical examination, as noted by several observers, was abdominal distention out of proportion to the probable duration of the obstruction and in striking contrast to the mildness of constitutional reaction. Tympanites sometimes appeared as soon as 1 to 2 hours after the ingestion of the obstructing food and frequently was the outstanding complaint of the patient who in other respects did not appear acutely ill.

Diagnosis. A correct pre-operative or *intravital* diagnosis was made only once in the 26 instances in which the true nature of the condition was made clear at operation or necropsy. Ackman describes a boy who rapidly ate whole cherries in competition with other children. Before operation an ileum beaded by cherry-stones could be felt both abdominally and by rectum, findings which made the diagnosis clear. The pre-operative or *intravital* diagnosis in the remaining 25 instances was usually intestinal obstruction of unknown etiology. In 2 cases acute appendicitis was suspected; in 2 obstructing carcinoma of the bowel; in 1 "adhesion ileus" as a sequel to operation for gastric ulcer performed 5 years previously; in 1 perforated gastric ulcer. The mortality for this whole group was 36 per cent.

There were 8 instances in which the diagnosis was suspected, and expectant treatment (enemata, intestinal antispasmodics) used with resultant recovery. This group is of particular interest. In a case reported by Brunzel the diagnosis was suggested by the presence of abdominal distention out of proportion to the duration of symptoms and by blood in the gastric contents. This author had a short time previously operated upon a patient with symptoms of acute obstruction and found only a tremendous distention of the small bowel. At necropsy in this instance the intestine showed extensive subserous bleeding and bloody fluid containing beans was found in the stomach. It was ascertained that this patient had been in the habit of using green beans in the preparation of "Uefangenelagers." Confronted later by a similar symptomatology, the diagnosis of "food ileus" was made and recovery followed conservative treatment. Brunzel stresses the importance of early and severe abdominal distention as the suggestive diagnostic sign, but admits the possibility of mistaken diagnosis in this second instance. He explains the gastric and subserous bleeding as due to the action of a substance derived from uncooked vegetables and given the name of phasin by Kobert. This substance causes agglutination of the erythrocytes leading to capillary stasis, cell diapedesis and eventually ulceration of the mucous membrane. Phasin, as Kobert's experiments show, is not present in cooked vegetables.

Willmoth, in the only pertinent report encountered in the literature of this country, describes 4 patients presenting the symptomatology of ileus but in whom the recovery by enemata of large amounts of undigested food particles with immediate improvement in the patient's condition suggested the continuance of conservative treatment. Recovery resulted. In 2 instances the enemata return contained large quantities of grape skins and seeds; in another, pieces of potato; in the fourth case popcorn was recovered over a period of a week. Although the diagnosis may be questioned, the description of these cases leaves the impression that these foods had actually caused obstruction.

If it be granted that the diagnosis was correct in this group of 8 cases, it is evident that conservative treatment is the method of choice in intestinal obstruction due to food. The mortality was 47.8 per cent in the group of 23 patients subjected to operation, while conservative measures resulted in recovery in every instance in which they alone were employed. While the diagnosis offers great difficulties, food ileus should be considered in a patient presenting signs of obstruction for which no cause can be ascertained, particularly if abdominal distention without signs of peritonitis, has become pronounced over a short length of time. A history of food digression during the preceding 24 hours might also be significant. Under such circumstances it would be justifiable to delay

operation until it had been amply demonstrated that the use of high enemata and intestinal antispasmodics was without avail.

The following case illustrates the significant features of this condition. So far as ascertainable it is the first instance of its kind, proved by operation and necropsy examination, to be reported in this country.

Case Report. A. S., an unmarried white male laborer, aged 36 years, walked into the Cottage Hospital Dispensary at 10 A.M. on October 25, 1930, complaining of nausea, pain in the abdomen and abdominal distention. The family and past histories were irrelevant. He had had no previous operations nor gastrointestinal symptoms. The patient had "ridden the brakebeams" from Oklahoma and had eaten no food during the journey. Arriving in southern California on the morning of October 23, he had slipped into an orange orchard and had rapidly eaten approximately 2 dozen oranges. About 4 hours later generalized cramplike abdominal pain appeared. He had a small bowel movement without relief. The following morning the cramps were more severe and he was nauseated, but did not vomit. He took a large dose of magnesium sulphate but had no further bowel movements and passed no flatus. Toward evening he noted that his abdomen was distended. The next morning the abdominal cramps were almost constant, most severe in the right lower quadrant. Persistent nausea was present, but no vomiting. His abdomen had become so distended that breathing was impeded. He entered the dispensary in an apprehensive state of mind and insisted that his overindulgence in oranges was the cause of his illness, a statement unfortunately ignored at the time.

The patient was exceptionally well nourished and developed, and did not appear acutely ill. The color was good, the pulse of good volume and tension at 90 per minute. The respirations were shallow, somewhat labored and numbered 35 per minute. The oral temperature was 98.6° F. Nothing of importance was found in the physical examination of the head and chest. The abdomen was tremendously distended, making evident the cause of the respiratory embarrassment. It was tympanitic with obliteration of liver dullness, and moderately tender to deep pressure throughout. There were no muscular guarding or rigidity, no palpable organs or masses, no fluid wave. On auscultation the abdomen was silent. Rectal examination was negative.

A stomach tube was immediately passed, and 3500 cc. of a brown fecal-smelling fluid removed. The patient felt better, but the distention was not appreciably decreased.

The laboratory reported a leukocytosis of 16,600, with neutrophilic polymorphonuclear leukocytes, 85 per cent; small lymphocytes, 12 per cent; large lymphocytes, 3 per cent. The urine contained a slight trace of albumin and 1 granular cast per high dry field.

A diagnosis of intestinal obstruction of unknown etiology was made, and at 12.30 P.M. laparotomy was performed by Dr. Irving Wills.

After opening the peritoneum about 300 cc. of clear straw-colored fluid were syphoned off. The small bowel and stomach were tremendously distended, the cecum and colon collapsed. The appendix was unaltered. The serosa of the terminal ileum was lusterless and beefy red. A doughy, movable mass was palpated, occupying its terminal 1½ feet. It was milked with considerable difficulty through two incisions made just proximal to the ileocecal valve. This mass after removal was found to consist of a compact collection of orange fiber and seeds. It was of sufficient bulk to fill completely the palms of two cupped hands.

The patient did well for 12 hours following operation, after which signs of peritonitis developed. He expired at 11 P.M. on the second postoperative night.

Necropsy was performed 10 hours after death by Dr. Richard Evans. The anatomic diagnoses were: Generalized acute fibrinous peritonitis; operative wounds of the ileum; surgical wound of the abdomen; cloudy swelling of the liver and kidneys.

On opening the abdomen no free fluid was present, but there were flecks of fibrin scattered over the peritoneal surfaces which were lusterless and injected. The stomach and small bowel were distended with gas. There was heavy fibrin deposition about the closed incisions in the terminal ileum. The mucosal surfaces of the gastrointestinal tract were unaltered except for congestion of the lower ileum. No perforation was found. There was no anatomic cause for intestinal obstruction. Culture of the heart's blood was sterile.

Conclusions. Intestinal obstruction caused by food is not rare, 39 instances having been reported since 1910. The case here described is the fortieth.

It may be caused by common articles of diet with a high content of indigestible material (skins, fiber, seeds) and is not necessarily dependent upon coexistent abdominal disease.

The site of predilection is the terminal ileum and the obstruction may be directly mediated by a spastic contraction of the bowel. The most common complications are perforation and peritonitis.

Symptoms appear on an average of 12 hours after the ingestion of the obstructing food and are those of acute small bowel obstruction with characteristically an early and pronounced tympanites out of proportion to the probable duration of the obstruction and the apparent good condition of the patient.

Confronted by this symptomatology in a patient in whom no apparent cause for obstruction is ascertainable, the diagnosis of "food ileus" should be considered, and possibly operation postponed until conservative measures have been proved of no avail.

Patients commonly diagnosed as having "acute gastroenteritis" or "ptomaine poisoning" may in reality have partial or transitory obstructions of this nature.

REFERENCES.

- Eichorst, H.: *Med. Klin.*, 1910, 2, 1559.
 Brunzel, H. F.: *Deutsch. Ztschr. f. Chir.*, 1928, 145, 1.
 Penkert, M.: *München. med. Wehnschr.*, 1919, 66, 100.
 Fink, F. V.: *Zentralbl. f. Chir.*, 1919, 46, 674.
 Walther, D.: *Ztschr. f. Chir.*, 1919, 151, 77.
 Scheele, K.: *Med. Klin.*, 1920, 16, 1178.
 Willmoth, A. D.: *Kentucky Med. J.*, 1921, 19, 188.
 Alexander, R. C.: *Edinburgh Med. J.*, 1929, 31, 617.
 Goebel, S.: *Zentralbl. f. Chir.*, 1925, 52, 1655.
 Loessl, J.: *Zentralbl. f. Chir.*, 1926, 53, 2327.
 Haselhorst, G.: *Zentralbl. f. Chir.*, 1926, 53, 1564.
 Griffiths, W. R.: *Med. J. Australia*, 1926, 2, 557.
 Metge, E.: *Zentralbl. f. Chir.*, 1927, 54, 3081.
 Chalmers, R.: *British Med. J.*, 1927, 1, 836.
 Wardill, W. E.: *British Med. J.*, 1927, 1, 56.

- Leusden, P.: *Med. Klin.*, 1928, 24, 1669.
 Krecke, A.: *Deutsch. Ztschr. f. Chir.*, 1929, 215, 336.
 Ackman, F. D.: *Canadian Med. Assn. J.*, 1929, 21, 710.
 Krauss, F.: *Zentralbl. f. Chir.*, 1929, 56, 2904.
 Seifert, E.: *Deutsch. Ztschr. f. Chir.*, 1930, 224, 96.
 Krückenberg, H.: *Zentralbl. f. Chir.*, 1930, 57, 387.
 Bir, H.: *Zentralbl. f. Chir.*, 1930, 57, 1219.

THE TREATMENT OF MEGACOLON BY PARATHORMONE.

WITH A REPORT OF THREE CASES.

BY LUTHER SHELDON, M.D.,

COMMANDER, M.C., U. S. NAVY,

RICHARD A. KERN, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,

AND

ERIC G. HAKANSSON, M.D.,

LIEUTENANT COMMANDER, M.C., U. S. NAVY,
 PHILADELPHIA.

(From the U. S. Naval Hospital, League Island, and the Medical Division of the Hospital of the University of Pennsylvania.)

A HITHERTO unobserved effect of parathormone upon the colon is herewith reported, as noted in 3 cases in which parathormone relieved the constipation incident to idiopathic dilatation of the large bowel (megacolon).

Case Reports. CASE 1.—E. G. B., a war veteran, aged 31 years, was admitted for the fifth time to the U. S. Naval Hospital, League Island, Philadelphia, on April 20, 1931, with a chief complaint of constipation. During infancy and childhood he enjoyed excellent health, except for an attack of measles at the age of 11, and typhoid fever at 15. His mother confirmed his statement that he had never suffered from constipation in early life. This symptom first appeared in 1917 when he was 18 years of age, at which time he first began to use laxatives. The trouble was not a distressing one and the average dose of cathartics would produce satisfactory defecation. In 1922, the patient had an attack of malaria, following which his constipation became much worse. In spite of large daily doses of purgatives, the bowels would move only once or twice a week. At about this time he began to have attacks of abdominal cramps associated with considerable distention of the abdomen. At such times he would obtain relief from the cramps by stooping and pressure on the abdomen; and from the distention, by large amounts of rhubarb. It is interesting to note that the distention was usually relieved in about an hour after taking the drug, although defecation did not result as a rule until the following day. He was first admitted to the U. S. Naval Hospital for a month in 1926, on which occasion the significant findings on Roentgen ray study of the gastrointestinal tract were "spastic antrum pylori and dilatation of the entire colon." He was readmitted in 1928 because of a continuation of his trouble, with

in addition certain nervous symptoms: restlessness, insomnia, mental depression.

The third admission was in May, 1929, and again for the same complaints. At this time, the opaque meal showed a delayed passage, most of it at the end of 24 hours being in the cecum, while a small portion was seen in the left half of the transverse colon, with an area of apparent constriction between. A barium enema reached the cecum, but a constricted area in the transverse colon was noted in all the films. He was discharged unimproved after three weeks, the diagnosis being "stricture of the colon."

The fourth admission was in October, 1929; his constipation had become worse and he had developed a complete inguinal hernia. A herniorrhaphy was performed and the patient was discharged a month later with his constipation unimproved.

He was admitted for the fifth time in April, 1931. During the intervening 18 months his constipation had continued unabated. Larger and larger doses of laxatives proved ineffective and the patient resorted to enemata of increasing size. The gallon was his unit of enema measure and he could retain 2 gallons without discomfort. The nervousness, insomnia and mental depression had continued and there was an increasing tendency to headache and backache. He had lost 20 pounds in a year. Roentgen ray again showed the huge colon but there was no evidence of stricture. Treatment consisted solely in palliative measures to relieve the constipation.

At this juncture, it occurred to one of us (L. S.) that parathormone might exert a favorable influence on the patient's colon. The thought was suggested by the beneficial effect of parathormone and calcium that Haskell and Cantarow¹ had observed in cases of chronic ulcerative colitis with diarrhea. Without any very clear-cut idea as to its expected mode of action, treatment with parathormone and calcium was begun on June 11, 1931. Ten units of parathormone were given hypodermically every other day and 5 grains of calcium lactate were given orally three times a day. At the end of a week no effect on the constipation had been produced, but the serum calcium had risen from 11 mg. to 12.5 mg. The parathormone was then increased to 10 units daily. During the second week he had one natural bowel movement, the first in over 10 years. In the third week his bowels began to move daily without laxatives or enemata. Headache, backache and drowsiness disappeared. He was discharged on July 6, 1931.

The parathormone dosage was then gradually reduced: for a week 10 units were given every other day, then once a week and on September 5 the parathormone was discontinued. The calcium lactate, 10 grains a day, was continued throughout. Daily bowel movements without laxatives occurred until 3 weeks after the parathormone was stopped, when he again found it necessary to resort to small doses of cascara. On October 10, he resumed parathormone treatment and took 50 units in 8 days but without effect. On November 10, he returned to the hospital for a barium enema which showed the dilated colon as on previous examinations. He then began taking 10 units of parathormone daily and after a week normal bowel movements were again established.

Since then he has taken several courses of parathormone, each course consisting of daily injections of 15 to 20 units for a period of about 3 weeks. During the second week of injections the bowels begin to move regularly and continue to functionate normally for about 3 weeks after stopping the injections. He does not take the parathormone continuously, partly because of a druggist's warning that increasing doses would be needed, and partly because of the expense. While taking parathormone he has more energy and endurance, his appetite improves and he gains weight.

He was last under observation on June 1, 1932. He was again in a bout of constipation, not having taken any parathormone for over a month. At

this time his serum calcium was 10.1 mg. A number of roentgenograms were made of various parts of the skeleton, including the hands. They showed no evidence of decalcification.

Case Summary. A man, aged 32 years, at the age of 18 developed chronic constipation which became increasingly severe. At the age of 27, he was found to have a hugely dilated colon and this finding was verified on subsequent examinations. For over 10 years he had no bowel movements without the aid of large doses of laxatives and enemata. Intermittent treatment with parathormone brought about normal bowel movements and has proved fairly satisfactory during one year. While no detailed studies of calcium metabolism have been made, the patient has not had abnormally low blood calcium figures before treatment nor unusually high figures during or after treatment. Roentgen ray shows no gross evidence of decalcification or other bone abnormality after one year.

CASE 2.—Mrs. M. P., a white woman aged 59 years, was admitted on the service of Dr. E. L. Eliason in the University Hospital on January 16, 1932, with a chief complaint of abdominal pain, distention and severe constipation. For several years she had suffered with flatulence and attacks of colicky pain in the abdomen, but without constipation. In the last 3 months the trouble became more severe and there was some difficulty in moving her bowels. On the day before admission there began an attack of abdominal colic, marked distention and obstinate constipation. Two enemata failed to remove gas or fecal matter. Her family physician sent her to the hospital with a tentative diagnosis of intestinal obstruction.

The past medical history was not significant. There was a story of mild recurrent joint pains, largely static in origin, probably as a result of a congenital luxation of the left hip.

The family history contained this significant item: Her mother had a peptic ulcer at the pylorus and died from an operation (gastroenterostomy) directed at this condition. Her one brother has had typical symptoms of duodenal ulcer for years. Of her 3 sisters, one has had duodenal ulcer for which a gastroenterostomy and pylorectomy were done.

The chief finding on admission was a greatly distended abdomen in which peristalsis of normal intensity was audible. The rectal examination was negative. There was no spasticity of the rectum sphincter.

She was given a barium enema right after her admission to the hospital. There was a huge dilatation of the lower rectum and sigmoid, this portion of the colon taking approximately 2 quarts of solution (Figs. 1 and 2). Then the colon became conical in shape and it was almost impossible to get the contents to go further. The contents were siphoned away in an effort to remove the enormous distention of the entire large bowel which was capacious and redundant. This was slightly effectual and it became possible to get a small amount of contents to enter the remaining loop of the redundant sigmoid, but it was impossible to evacuate this part of the colon. The roentgenologist made a diagnosis of probable carcinoma in the middle of a redundant sigmoid.

The patient was then taken to the operating room where a cecostomy was performed. The cecum was found to be very greatly distended. Following the cecostomy, the patient's condition improved rapidly. Gas and fecal matter were evacuated freely through the cecostomy opening, and the abdomen became soft.

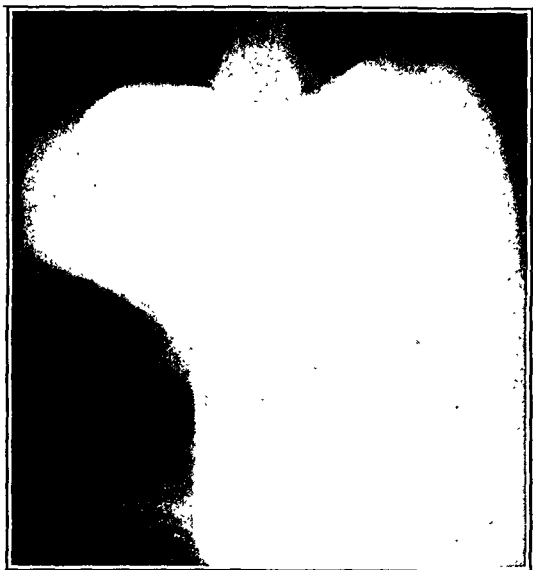


FIG. 1



FIG. 2

FIGS. 1 and 2.—Both films were made at the first admission of Case 2 on January 16 and show respectively the upper and lower portions of the greatly dilated rectum and sigmoid, beyond which the enema would not pass. The degree of overlapping of the regions covered by the films may be seen by comparison of bony landmarks. The size of the remainder of the large bowel is obvious from its gas-filled loops.



FIG. 3.—Second barium enema on January 23, one week after cecostomy, shows the same apparent obstruction in the sigmoid beyond which the opaque material passed with difficulty. Enormous ballooning of the entire colon, 4 to 6 quarts of enema being injected. After much manipulating and siphoning, contents were made to pass into the rest of the large bowel and some opaque material appears in the descending colon. (A third barium enema on April 27, at a time when the patient had greatly reduced her parathormone dosage and was having clinical evidences of obstruction, showed a picture similar to Fig. 3.)



FIG. 4.—Barium enema on May 5, after 8 days of intensive parathormone treatment with complete clinical relief: the enema passed readily to the cecum and less than 2 quarts filled the whole large bowel which is obviously much less capacious than before.



FIG. 5.—Film made immediately after evacuation of the enema shown in Fig. 4. The size of the lumen of the colon is practically within normal limits.

On January 23, a second barium enema study was made. The same constriction in the sigmoid was found as on the previous examination. There was an enormous ballooning of the entire colon, 4 to 6 quarts of enema being injected (Fig. 3). After much manipulation and siphoning it was possible to get the contents to pass into the cecum and out through the cecostomy. The roentgenologist again made a diagnosis of probable carcinoma in the middle of the sigmoid.

On January 25, a laparotomy was performed. The whole colon was enormously distended. A portion of the small intestine with its mesentery overlay the descending colon and was apparently responsible for the acute obstruction of the colon. A careful search of the entire bowel showed no evidence of neoplasm or other obstruction. The small bowel was returned to its normal position and the abdomen was closed.

After operation, the chief concern was to combat her abdominal distention and constipation. The use of external heat, laxatives, pituitrin and enemata proved only moderately successful, there being frequent attacks of distention, especially after meals. The cecostomy tube was clamped off for a few days at a time, until the movements by the normal route became more satisfactory and on February 12 the tube was removed. She was discharged to her home on February 16, 1932, but 6 days later she returned to the hospital. There had been no normal bowel movement, and cathartics, while they produced evacuations, did not relieve the distention.

At this time, one of us (R. K.) first saw the patient and suggested the use of parathormone. On February 24, injections of parathormone, 10 units t.i.d., were begun. The patient was also given calcium gluconate, 30 grains twice a day. She continued to take cascara and agarol as before. On the following day the distention of the abdomen was less marked. Two days later her bowels moved without an enema. She left the hospital on February 27. Two days later the laxatives were discontinued, as her bowels were moving spontaneously twice daily and the abdominal distention had disappeared.

The parathormone dosage was then gradually reduced, first to 20 units and then to 10 units daily. The bowels continued to move daily without laxatives. On one occasion, after eating freely of corn pone, she experienced an attack of abdominal distention but was relieved in a few hours after taking an extra dose of parathormone. She again tried to reduce the dosage, taking only 10 units every other day. Within a week there was a return of abdominal distention and on 2 days her bowels failed to move. A daily dose for 5 days gave only partial relief. On March 17 the dose was increased to 10 units twice a day and on March 21 to 10 units three times a day for 3 successive days. This resulted in an increased number of bowel movements, 2 or 3 a day, so that the parathormone dosage was again reduced to 20 units a day. The increased number of bowel movements, however, continued for several days, there being 6 on March 27. All of these movements were copious formed stools of normal consistency.

On March 29, she was taking 10 units of parathormone and 30 grains of calcium gluconate a day. At that time the abdomen was soft and flat. The serum calcium was 10.5 mg.

In the following month she again reduced the dose of parathormone to 10 units every other day. For a time she experienced no difficulties and the bowels continued to move once or twice daily.

On the 26th of April there was a sudden return of abdominal distention, attributed by the patient to overeating of a fruit salad. There was no bowel movement on that or the following day. When cramps appeared, she summoned her family physician who found her abdomen hugely distended. A number of enemata were ineffectual. Three doses of parathormone (10 units each) had no apparent effect. Fearing that there was an

acute intestinal obstruction, her physician returned her to the University Hospital on the evening of April 27.

On admission, the outstanding finding was a hugely distended abdomen in which exaggerated peristalsis was audible. A barium enema showed the same hugely dilated colon that had been observed on previous occasions. A 2-quart enema merely filled the sigmoid, while small quantities of the opaque material passed higher into the descending colon as a result of external pressure on the abdomen. In the course of the fluoroscopic study evidences of returning intestinal tone were observed in the form of localized contractures in several parts of the large bowel. The opaque enema was alternately injected and removed by siphoning a number of times, and each time a considerable amount of gas was drawn off. It was decided to postpone laparotomy and to return to more active parathormone treatment.

That night she passed a great deal of gas by bowel and on the following morning her abdomen was soft. Parathormone was given in 10 unit doses t.i.d. for the next 6 days, during which time her bowels moved with increasing freedom, reaching 5 movements on May 3. These movements were all formed. The parathormone dosage was then reduced to 20 units daily.

On May 5, another barium enema study was made (Fig. 4). The contents passed up into a long high loop of the sigmoid which was just to the right of the midline. Then the contents passed through the redundant portion of this loop down to the right in the sigmoid and then across the abdomen to the left side up into the descending colon, thence into the transverse colon and the cecum. The transverse colon seemed to be posterior to the sigmoid. This seems to offer another explanation for the obstipation, in that distention of the rectum and of the transverse colon might press upon the redundant loop of sigmoid. The lumen of the colon was considerably less capacious than that seen in any other examination, less than 2 quarts of enema material filling the whole large bowel. After evacuation most of the contents had been expelled and *the lumen of the colon was practically within normal limits* (Fig. 5).

Roentgenograms of various parts of the skeleton on May 6 showed no evidence of decalcification. The serum calcium on that date was 10.5 mg.

Since then, the patient has been in excellent condition. She is taking 20 units of parathormone and 30 grains of calcium gluconate daily. The bowels are moving two, occasionally three times daily and without laxatives. When seen on June 8, she claimed she felt better than for years. Her abdomen was flat and soft. Her weight was 112 pounds, a gain of 10 pounds in 6 months. The serum calcium was 11.6 mg.

Case Summary. A woman aged 59 years, had had increasing constipation, abdominal distention and cramps for about 2 years. A sudden increase of trouble led to a diagnosis of acute colonic obstruction and an emergency cecostomy was performed. Barium enema studies suggested a carcinoma of the transverse colon but laparotomy showed only a hugely distended large bowel. Parathormone injections resulted in a return of normal bowel movements. When the parathormone dosage was greatly reduced 3 months later, signs and symptoms of colonic obstruction recurred and laparotomy was again considered. Under increased parathormone dosage, normal bowel movements were reestablished and the entire large bowel was shown 8 days later to have been reduced to practically normal size. The patient did not show any unduly low serum calcium figures before treatment, nor any very high serum calcium

figures after treatment. The skeleton showed no Roentgen ray evidence of decalcification after more than 4 months of parathormone therapy. There is an interesting family history of peptic ulcer, a condition which by some has been related to a possible hypoparathyroid state.

CASE 3.—I. S., a man aged 65 years, was admitted on the service of Dr. I. S. Ravdin in the University Hospital on April 9, 1932, with a chief complaint of abdominal pain. He had been well until 5 weeks previously, when he developed generalized abdominal pain, mild at first and intermittent. The symptoms became gradually worse, with increasing pain, abdominal distention and constipation. Saline laxatives were effectual but did not lessen the pain. On April 6 the pain became more marked, especially in the right side, constipation became obstinate and he vomited once after taking Epsom salts. On April 9 he was sent to the hospital with a tentative diagnosis of intestinal obstruction.

Physical examination showed a rather distended abdomen with moderate tenderness, especially in the right half of the abdomen, but without rigidity. Peristaltic sounds were if anything reduced in degree. Rectal examination was negative.

A barium enema study showed marked gaseous distention of both small and large intestine. There was no evidence of obstruction or growth involving the large bowel. The whole colon was capacious, redundant and atonic, but "there were areas suggesting spasm."

He was first seen by one of us (R.K.) on April 11. The obstinate constipation and abdominal findings as above noted were unchanged. The serum calcium was 7.8 mg. Parathormone treatment, 10 units t.i.d., were begun on that day. On April 12, the patient had two spontaneous bowel movements, his first in several weeks. His condition returned rapidly to normal and during the rest of his stay in the hospital he continued to have 1 or 2 bowel movements daily. The stools were always formed and of normal consistency. On April 15, the serum calcium had risen to 10.4 mg. He was discharged on April 16 in good condition. For a few days he received parathormone injections at home but then refused further treatment. When last heard from on June 10 he was beginning to have trouble again with abdominal discomfort and constipation.

Case Summary. A man, aged 65 years, developed gradually over a period of 5 weeks an adynamic ileus of unknown origin. The chief findings were abdominal distention, a capacious redundant atonic colon (barium enema) and a low serum calcium level. Parathormone injections were followed by a return of normal bowel movements with attendant relief of symptoms and a return to normal of the serum calcium.

Discussion. *The relation of the parathyroids to the motor function of the gastrointestinal tract.* The question which naturally presents itself is, in what way are the parathyroids connected with gastrointestinal motor function? That such a relation exists has been suggested in the past by a number of clinicians, to some of whose writings we shall refer. Attention has been directed especially to the upper digestive tract and the possible part that parathyroid deficiency may play in the etiology of peptic ulcer. Grove and Vines² reported a number of cases of gastric and duodenal ulcer in

which there was a low serum calcium level and in which a parathyroid extract was said to have been useful in treatment. Since, then, numerous reports have appeared, especially in the European literature, on the efficacy of parathormone in the treatment of peptic ulcer. The use of parathormone in peptic ulcer has been predicated on its relaxing effect on a spastic pylorus and pyloric antrum, as well as the finding in some cases of a low serum calcium level. While the results have been satisfactory in less than half the cases so treated,³ they at least point to a more than merely coincidental presence of ulcer and parathyroid deficiency in some of these patients. Alkan,⁴ whose interest in the subject was aroused by the observation in a patient, a woman aged 39 with tetany and gastric ulcer, that spasm of the gastric antrum was relaxed by parathyroid therapy, reports that of 145 cases of tetany observed by him, 45 per cent had peptic ulcer. We recall the fact that the mother and two of the four siblings of our case 2 had peptic ulcer. Higgins⁵ has reported a patient with tetany in whom both on Roentgen ray study and at operation there was found an obliterative spasm of the small bowel. Aub and Salter⁶ found that the spastic colitis due to lead poisoning could be lessened and its pain relieved by parathormone. Timme⁷ observed a "spastic colitis" with constipation in patients with a low serum calcium level (but not low enough to produce tetany). Mahler and Beutel⁸ found that parathormone was useful in some cases of spastic constipation and mucous colitis, but they were unable to state criteria as to which types of cases would be benefited. These authors also cite Businco to the effect that in insufficiency of the parathyroids he observed spasms of the digestive tract with constipation. Haskell and Cantarow¹ pointed out the usefulness of parathormone in the treatment of chronic ulcerative colitis.

On the other hand, the literature on the clinical picture of parathyroid disorders rarely refers to involvement of the digestive tract. In the many case reports of hypoparathyroidism, there is occasional mention of vomiting or abdominal cramps, but the state of the bowels is rarely recorded. Boothby, Haines and Pemberton⁹ in their comment on observations in 88 cases of postoperative parathyroid insufficiency make no mention of gastrointestinal disorders. In the reports of some cases there is only a note as to the diarrhea which existed previous to the operation for the hyperthyroid state, and nothing is said of the bowels during the parathyroid insufficiency. Cases of diarrhea with low serum calcium and tetany are not pertinent to the question, since the low calcium and the tetany are secondary to the diarrhea (lack of calcium absorption) and are not due to parathyroid deficiency. There is the same paucity of information as to the gastrointestinal tract in hyperparathyroid conditions. Barr and Bulger¹⁰ make no mention of the digestive tract in discussing the clinical syndrome of hyperparathyroidism. Con-

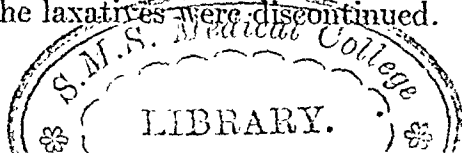
stipation has been reported in a few cases of hyperparathyroidism,^{11,12,13,14} but was at times associated with and perhaps due to vomiting.^{11,12} We have found no case report in which hyperparathyroidism was associated with diarrhea.

There is very little experimental evidence as to the effect of the parathyroid hormone on the digestive tract. Carlson and Jacobson¹⁵ reported that of 23 parathyroidectomized dogs, 19 showed congestion of the mucosa in the pyloric portion of the stomach and the beginning of the duodenum. Mahler and Beutel⁸ in 40 human subjects found that in most instances parathormone had no noteworthy effect on the peristalsis of stomach and colon beyond an occasional deepening of the peristaltic waves, and at times an increase in the speed of stomach emptying. In most cases there was a depression of the tonus of stomach and colon, more marked in patients with spastic intestinal conditions than in normals. Johnson and Wilder¹⁶ observed no digestive tract symptoms in a human subject in whom hyperparathyroidism was induced by large doses of parathormone. Rose, Stucky and Cowgill¹⁷ observed no significant effect of parathormone on gastric atony in dogs with B-avitaminosis. In one normal dog there occurred a slight depression of gastric tone.

These data would suggest that disorders of the digestive tract, especially altered motor activity, are not a frequent manifestation of parathyroid malfunction and that they have no definite relation to hyper- or hypofunction of these organs. On the other hand, it is possible that the interest of observers has been focused so largely on the major phenomena of parathyroid diseases, such as striped-muscle changes (tetany, hypotonicity), and abnormalities in calcium metabolism and related skeletal disorders, that the less striking gastrointestinal changes have been overlooked or misinterpreted. It may be possible, too, that some cases of postoperative parathyroid insufficiency have been reported before striking gastrointestinal changes have had time to develop.

Of great interest in this regard is one of the cases cited by Boothby, Haines and Pemberton,⁹ a woman who developed symptoms of chronic parathyroid insufficiency after a thyroidectomy in 1917. *In 1923, gastrointestinal distress with chronic stasis led to resection of 7.5 cm. of ileum, the appendix, cecum, ascending colon, hepatic flexure and two-thirds of the transverse colon.* Yet the authors do not suggest any relation between the parathyroid insufficiency and the intestinal disorder.

Of interest, too, is the case of a patient recently observed in the University Hospital and reported by Hitzrot and Comroe.¹⁸ A woman with hyperparathyroidism complained of constipation and required daily laxatives during 10 weeks of observation. Three days after parathyroidectomy symptoms of hypoparathyroidism appeared and the laxatives were discontinued. Her bowels moved



normally during the next 15 weeks in the hospital during which time she received parathormone. After 6 weeks at home during which she received a lower dose of parathormone and calcium she returned to the hospital with latent tetany and with constipation that required the daily use of laxatives. In yet another patient with idiopathic parathyroid insufficiency recently observed in the University Hospital there were noted constipation, abdominal discomfort, and on Roentgen ray study, dilatation of the lower half of the duodenum, jejunum and most of the ileum with a curious pooling of the opaque contents, marked haustral indentations in the sigmoid and some narrowing of the rectum. The administration of calcium in large doses, or of parathormone, not only relieved the tetany but also the constipation and the abdominal discomfort.

It is perhaps significant that both the clinical and the experimental data, meager though they be, are in agreement with the anticipated effect of excess or insufficiency of parathyroid hormone on intestinal motility: constipation due to intestinal atony in hyperparathyroidism, and constipation due to intestinal spasticity in hypoparathyroid states.

The relation of the parathyroids to megacolon. Of the various etiologic factors which have been proposed to explain megacolon, perhaps the most acceptable is that of a neuromuscular dysfunction, in which spasms in sphincter regions (rectal, pelvirectal) are attended or followed by dilation proximal to the spastic areas. This is the rationale for the successful treatment of megacolon suggested by Royle and Hunter¹⁹ who by ramisectomy reduced sympathetic stimuli to the bowel, and by Judd and Adson²⁰ who performed lumbar sympathetic ganglionectomy and ramisectomy. An important point is that the muscle of the dilated bowel is not atrophied but decidedly hypertrophied. This makes it possible for the bowel to contract with remarkable promptness (minutes!) when these sympathetic stimuli are abolished by spinal anesthesia, as shown by Judd and Adson²⁰ and Scott and Morton.²¹ That parathormone can effect a contraction of the dilated colon is shown by the Roentgen ray findings in our Case 2, but how this effect is produced we are unable to say. The slowness with which this effect is brought about at least suggests that the action is not a direct one upon the intestinal musculature but perhaps through some intermediate mechanism, possibly on calcium metabolism. That hypoparathyroidism plays an etiologic rôle in the causation of megacolon is as yet an unwarranted assumption. The meager evidence at hand is only suggestive. Our Case 3 and the case of Boothby, Haines and Pemberton above referred to are the only ones in which to our knowledge a low serum calcium has been found. In our other 2 cases the serum calcium was normal, but the fact that it rose only slightly under parathormone administration may be significant. In none of a considerable number of case reports of megacolon did we find any mention of the serum calcium level.

It is suggested that in the future patients with megacolon be studied from the standpoint of a possible low-grade chronic parathyroid deficiency. There is also an obvious need for further experimental investigation of the action of parathormone on the motor function of the digestive tract. Such studies are at present being carried out in dogs.

The treatment of megacolon. Resection of the dilated bowel as formerly practised was a mutilating operation with a high operative mortality. The introduction of lumbar sympathetic ganglionectomy and ramisectomy was a great step forward in that these procedures can be performed at comparatively little risk. They are however open to the criticism that they do not remove an underlying cause. Whether the parathormone treatment of megacolon will prove acceptable still remains to be seen. Its efficacy in the cases presented at least warrants its further trial. In our Cases 2 and 3 it made it possible to avoid a dangerous emergency operation for a supposed intestinal obstruction. The possible dangers to patients which prolonged parathormone administration may involve require thorough study.

Summary. 1. It has been observed in 3 cases that constipation due to idiopathic dilatation of the colon is relieved by parathormone.

2. In one instance the treatment has proved effective for one year.

3. In one patient it was shown by Roentgen ray that a hugely dilated colon was reduced in 8 days to practically normal size.

4. The possible relation of abnormal parathyroid function to disorders of intestinal motility and to megacolon is discussed.

5. Further studies are indicated to determine (a) the possible dangers to patients from prolonged parathormone administration, and (b) the mode of action of parathormone on intestinal motor functioning as disclosed by clinical studies and by animal experimentation.

REFERENCES.

1. Haskell, B., and Cantarow, A.: Calcium and Parathyroid Therapy in Chronic Ulcerative Colitis, *AM. J. MED. SCI.*, 1931, 181, 180.

2. Grove, W. R., and Vines, H. W. C.: Calcium Deficiencies, their Treatment by Parathyroid, *Brit. Med. J.*, 1922, 1, 791.

3. Moutier, F., and Camus, L.: Recherches sur le traitement de l'ulcère de l'estomac par l'hormone parathyroïdienne, *Arch. d. mal. de l'app. digestif*, 1929, 19, 1237.

4. Alkan, L.: La tétanie viscérale, *Arch. d. mal. de l'app. digestif*, 1931, 21, 813.

5. Higgins, W. H.: Abdominal Manifestations of Tetany, *Virginia Med. Monthly*, 1930, 56, 653.

6. Aub, J. C., and Salter, W. T.: Cited by Timme.⁷

7. Timme, W.: Some Clinical Aspects of a Diminished Calcium Utilization, *Endocrinology*, 1931, 15, 442.

8. Mahler, P., and Beutel, A.: Zur Wirkung des Epithelkörperchenextraktes auf Tonus und Peristaltik des Magens und Darms, *Endokrinologie*, 1931, 9, 17.

9. Boothby, W. M., Haines, S. F., and Pemberton, J. de J.: Postoperative Parathyroid Insufficiency, *AM. J. MED. SCI.*, 1931, 181, 81.

10. Barr, D. P., and Bulger, H. A.: *The Clinical Syndrome of Hyperparathyroidism*, *Am. J. Med. Sci.*, 1930, 179, 449.
11. Pemberton, J. de J., and Geddie, K. B.: *Hyperparathyroidism*, *Ann. Surg.*, 1930, 92, 202.
12. Bergstrand, H.: *Ostitis fibrosa generalisata Recklinghausen mit pluriglandulaerer Affektion der innersekretorischen Druesen und roentgenologisch nachweisbarem Parathyreoideatumor*, *Acta med. scand.*, 1931, 76, 128.
13. Hannon, R. R., Shorr, E., McClellan, W. S., and Du Bois, E. F.: *Case of Ostitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of Parathyroid Bodies: Metabolic Study*, *J. Clin. Invest.*, 1930, 8, 215.
14. Lievre, J. A., and Muller, P.: *Case of Parathyroid Tumor*, *Bull. et mém. Soc. med. d. hôp. de Paris*, 1931, 47, 1515.
15. Carlson, A. J., and Jacobson, E.: Cited by Alkan.⁴
16. Johnson, J. L., and Wilder, R. M.: *Experimental Clinical Hyperparathyroidism: Metabolism Studies in Man*, *Am. J. Med. Sci.*, 1931, 182, 800.
17. Rose, W. B., Stucky, C. J., and Cowgill, G. R.: *Effect of Parathormone on Gastric Motility in Vitamin-B Deficient and Normal Dogs*, *Am. J. Physiol.*, 1930, 92, 554.
18. Hitzrot, L. H., and Comroe, B. I.: *Hyperparathyroidism Without Parathyroid Tumor: Report of a Case Improved by Partial Parathyroidectomy*, *Arch. Int. Med.* (in press).
19. Royle, N. D., and Hunter, J. I.: *Symptomatology of Complete Transverse Lesions of Spinal Cord: Experimental Study*, *Australian J. Exp. Biol. and Med. Sci.*, 1924, 1, 57.
20. Judd, E. S., and Adson, A. W.: *Lumbar Sympathetic Ganglionectomy and Ramisection for Congenital Idiopathic Dilatation of Colon*, *Tr. Am. Surg. Assn.*, 1928, 46, 159.
21. Scott, W. J. M., and Morton, J. J.: *Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease*, *J. Clin. Invest.*, 1930, 9, 247.

POST-VACCINAL ENCEPHALITIS.*

BY A. H. GORDON, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, MC GILL UNIVERSITY; PHYSICIAN TO THE MONTREAL
GENERAL HOSPITAL,

AND

LAWRENCE J. RHEA, M.D.,

ASSOCIATE PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY; DIRECTOR OF THE DEPARTMENT OF PATHOLOGY, THE MONTREAL GENERAL HOSPITAL,
MONTREAL, CANADA.

(From the Medical Services and the Department of Pathology, The Montreal General Hospital.)

IN 1929, Dr. Simon Flexner brought before this Association the subject of Post-vaccinal Encephalitis and discussed it from various angles. Up to that time only a very few cases had been recognized in the United States and none in Canada, but epidemics of the disease had occurred in other countries. The largest epidemics of the disease had been in England and Holland. Other countries which had small epidemics were Austria, Germany and Norway, and

* Read at annual meeting of the Association of American Physicians, Atlantic City, May 2, 1931.

scattered cases had been seen in France, Sweden, Russia, Switzerland, Poland and Jugo-Slavia.

In the report of the Ministry of Health of Great Britain upon this subject in 1930 it was stated that no cases had been reported in Australia, Africa or Asia. A few cases had been noted in the United States, but none so far in Mexico, Central America or Canada.

On hearing Dr. Flexner's paper a case that was under the care of one of us came to mind. We have no notes of the case but a very pungent memory of it remains.

Case Reports. CASE 1.—A child, aged 6 years, who, after vaccination, developed a very sore arm within a week, complained of headache and vomiting and became very drowsy and feverish. She showed well marked retraction of the neck and a tentative diagnosis of tuberculous meningitis was made. After a week she recovered from her acute illness but was a long time getting well. We are convinced that she suffered from post-vaccinal encephalitis.

Dr. Flexner's address also reminded us of the following case, which is apparently the first to be reported from Canada:

CASE 2.—A boy, aged 11 years, who had been well and strong up to the onset of this illness was brought into The Montreal General Hospital unconscious on August 11, 1928.

He had mumps, measles and chickenpox in infancy; otherwise his history was negative.

The parents stated that he had been suddenly seized with a severe headache on a Sunday night and that this had continued throughout Monday and Tuesday and was accompanied by vomiting.

On Wednesday morning he became unconscious and was brought to the hospital.

When seen he could be partially aroused but would not answer questions. He lay on his left side with his head bent forward and both hips and knees flexed. He was restless and every 5 minutes or so would throw himself about in bed.

The pupils reacted sluggishly to light, the left was somewhat dilated and there was ptosis of the left eyelid.

The eyes were kept partially open and responded but little to stimuli. There was no disease found in the ears or in the mastoid regions and there was no sign of head injury. The ocular fundi were normal.

There was some spasticity of both arms and legs, the neck was somewhat rigid and Kernig's sign was slightly present.

The abdominal reflexes were absent, the knee jerks were present and a well defined bilateral Babinski phenomenon was elicited. On the following day the knee jerks could not be obtained.

There was incontinence of both urine and feces.

On admission there was herpes on both lips. The pulse rate was 90, the respirations 16 and the temperature which was 100.2° F. on admission, rose steadily to 107° before death 2 days later.

The right arm and leg developed a marked degree of spasm and a lateral nystagmus appeared. Later the spasm passed into flaccidity and complete unconsciousness developed.

Respirations became more rapid and dullness and râles appeared at the bases of both lungs.

For some time before death the head and eyes were turned toward the right and both pupils became much contracted.

Lumbar puncture on two occasions gave a clear fluid not under tension, containing no cells and only a faint reaction for globulin and a negative reaction for sugar. Culture of the fluid was negative.

Blood examination showed hemoglobin 75 per cent, red cells 4,800,000; leukocytes on three counts, 8000, 7700 and 7800 per c.mm.

Vaccination history: The family had recently removed from another Province and as the child had not been vaccinated he could not enter school. Twelve days before the onset of the illness, vaccination by the scratch method was done in one area on the left arm.

On admission the scab which was hard and dark brown, was about 2 cm., in diameter, with quite marked redness and induration about it. The left axillary glands were enlarged and tender.

The progress notes upon the case are of interest. On the day of admission the following note was made: "The case has all the appearances of a meningeal reaction but the character is hemiplegic and the predominance of weakness over rigidity is noticeable. This, with the practically negative spinal fluid suggests some unusual cerebral infection and vaccinia is suggested."

The diagnosis made shortly before death was as follows: "Some type of spreading encephalitis—poliomyelitis superior is suggested, with the predominant lesion in the left cortex. Terminal bronchopneumonia. The terminal myosis and fixed pupils suggest a basal lesion."

Necropsy. A very limited postmortem was performed 2½ hours after death. Permission could not be obtained to examine the brain. The spinal cord could be examined only from the third cervical to the lumbar region.

Many microscopic sections were examined from various areas in the cord. The following is the histologic report upon them:

"Some of the sections show a quite normal condition; the neuroglia is intact; the vessels are normal; the nerve cells, dendrites, axones and nerve fibrils are well preserved. There are areas in the cord, however, which show lesions of varying intensity in the cord substance. There are numerous areas, more marked in one-half of the cord than in the other, where demyelination is very prominent. These areas appear as discrete and confluent patches. In the discrete areas one notes that this lesion occurs as a ring-like area about a bloodvessel. The demyelination is more marked throughout the anterior portion of the cord than in the posterior portion. In some of the sections a similar lesion is seen along each side of the anterior commissure as a zone of varying length and breadth. As a whole, there is not much cellular infiltration of the demyelinated areas. In certain places, however, these areas do show quite a marked infiltration with cells."

The other organs of the body showed no gross lesion except in the lungs, where there was congestion and areas of acute bronchopneumonia.

Microscopically, there was a general vascular congestion of the kidneys, particularly marked in the medulla. The convoluted tubules showed cloudy swelling.

Sections of the excised vaccination area showed superficial ulceration and a scab consisting of necrotic material.

Extending through the skin and into the subcutaneous tissue there was a diffuse inflammatory exudate and necrotic foci. The cellular exudate was composed of lymphocytes, plasma cells, endothelial cells and enormous numbers of eosinophils.

Discussion. A considerable body of information has grown up concerning post-vaccinal encephalitis but there are still many gaps in our knowledge.

The morbid anatomy and histology are fairly well clarified and Perdrau, Turnbull and McIntosh and others have set out the features distinguishing this disease from poliomyelitis on the one hand and encephalitis lethargica on the other.

There are certain aspects of the microscopic lesion of poliomyelitis, post-vaccinal encephalitis and encephalitis lethargica that are similar, yet there are certain lesions which seem to differentiate these three diseases. The accompanying illustrations demonstrate especially these differentiating features.

Fig. 1 is from a clinical case of encephalitis lethargica. It shows a bloodvessel dilated with blood. About it is a very distinct encircling zone infiltrated with cells, most of which are of the lymphocytic series. The slide shows this alone. None of the areas of softening that have been described in encephalitis lethargica are present. Perivascular lymphocytic collars are not diagnostic of encephalitis because they appear in other acute diseases of the central nervous system, one of which is post-vaccinal encephalitis.



FIG. 1.—From a clinical case of encephalitis lethargica showing perivascular collar of cells. (From Boyd's Pathology of Internal Medicine.)

Fig. 2 is from a clinical case of anterior poliomyelitis. The microphotograph is taken so as to include a portion of the anterior horn and the adjacent white matter. One intact motor nerve cell and the sites of two others are seen. The latter areas contain numerous phagocytic cells which have almost completely removed the two nerve cells that have been destroyed by the virus of poliomyelitis. There is no demyelination. We do not think that this lesion has been described in association with post-vaccinal encephalitis, and we have never seen it except in clinical cases of poliomyelitis.

Fig. 3 is from our case of post-vaccinal encephalitis. This shows the microscopic lesion which is said to be characteristic of the dis-

ease—areas of demyelination. In this particular case these areas are more numerous in one-half of the cord, are discrete and confluent and in the center of some of them a dilated and engorged blood-vessel is distinctly seen.

Fig. 4, also from our case and near the same site as Fig. 3, shows very marked demyelination and like the former slide there are dilated vessels with areas of demyelination about them.

Fig 5, also from our case of post-vaccinal encephalitis, is a high power photograph of a small area of demyelination in the gray matter. It shows infiltration of an area of demyelination with cells.

Figs. 2, 3 and 4 demonstrate the microscopic lesions which are claimed by Turnbull and others to be characteristic of post-vaccinal encephalitis.

Microscopically the general character of the lesion of post-vaccinal encephalitis is that of a meningo-encephalitis. The meninges are infiltrated with small lymphocytes, plasma cells and large cells of endothelial origin. While the meningitis is slight it can be traced down over the cord.

Infiltration of the perivascular space—the so-called lymphocytic collar or sleeve of the type seen in epidemic encephalitis—is the commonest lesion present, but this feature is shared with both epidemic encephalitis and poliomyelitis. The striking feature of the post-vaccinal disease is the presence of areas of demyelination extending for some distance around the vessels and unassociated with vascular thrombosis.

Demyelination is an essential feature of this extra adventitial softening and the lesions have the punched out appearance of those in disseminated sclerosis.

Thus demyelination appears to be the primary lesion and cellular infiltration is secondary.

The good state of preservation of the ganglion cells is noticeable in the post-vaccinal affection as compared with poliomyelitis, in which they bear the brunt of the attack.

Other diseases which have shown areas of demyelination are the encephalomyelitis of measles, smallpox, antirabies inoculation, Schilder's disease and to some extent disseminated sclerosis.

The clinical features are fairly illustrated by the case above described. The onset is sudden and stormy with headache, vomiting, fever and convulsions. Paralysis and coma are common. Meningeal signs and cranial nerve palsies may also appear.

The cerebrospinal fluid may show neither globulin nor increase of cells.

It is quite possible that some cases diagnosed as tetanus following vaccination may have been cases of *encephalomeningitis*. One of us has seen what is probably such a case. No postmortem was obtained, but a bacteriologic examination of the material from the vaccination was negative for *B. tetani*.

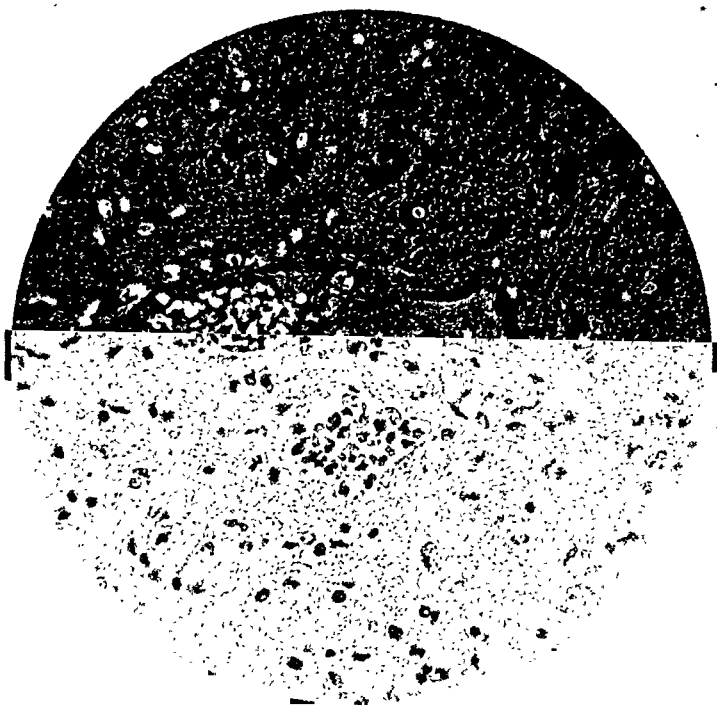


FIG. 2.—Anterior poliomyelitis. Portion of anterior horn with adjacent white matter to show one nerve cell intact; the sites of two others are represented by great numbers of phagocytic cells. Note the absence of demyelination.

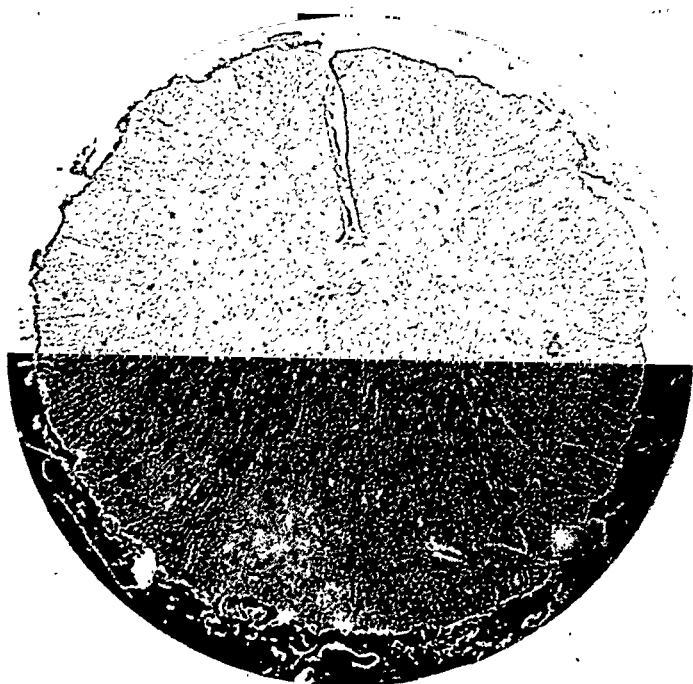


FIG. 3.—Post-vaccinal encephalitis. To illustrate areas of demyelination, in the centers of some of which a widely dilated bloodvessel is seen.

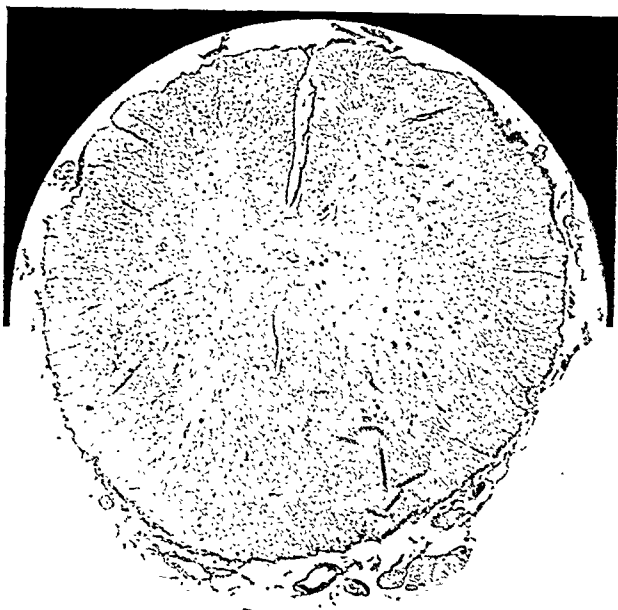


FIG. 4.—Post-vaccinal encephalitis. Transverse section of cord showing demyelination most marked throughout one-half of the cord.

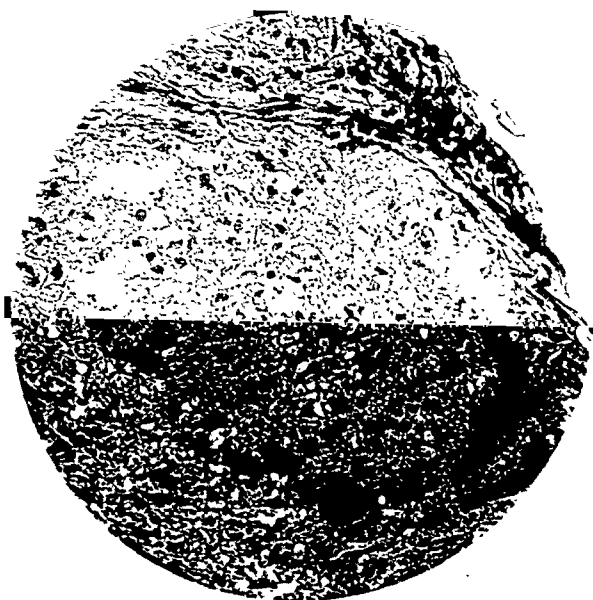


FIG. 5.—Post-vaccinal encephalitis. Cellular infiltration in an area of demyelination. High power.

The mortality in the Dutch cases was 35 per cent and in the English cases 50 per cent, but in the cases which recovered, the recovery was complete. Two weeks, as a rule, sees either death or improvement.

H. H. Donnelly, of Washington, reports 5 cases occurring during October, 1930, following primary vaccination in children 6 and 7 years of age all of which recovered completely.

All had presented clinical evidences of more or less severe encephalomyelitis.

The onset in 3 cases was at the peak of the vaccination and in the other 2 it appeared during the fourth week after inoculation.

The age incidence in the Holland group was overwhelmingly between 3 and 7 years, but the 93 English cases had 14 above 15 years of age and the balance fairly well spread out from 1 year to 15.

It had been thought that infants were practically immune but recently McNair Scott has collected 22 cases under 6 months old. Among these the mortality was 54 per cent.

The incubation period between vaccination and the development of symptoms is, in the great majority of cases, from 10 to 14 days. Eighty-seven out of 123 of the Dutch cases and 71 out of 87 English cases fall into this group.

McNair Scott points out that cases of post-vaccinal encephalomyelitis are more common in countries where vaccination is declining than in those in which the proportion of vaccinated persons is high.

It would seem now that a very constant pathologic anatomical picture has been shown to occur in the encephalitis following vaccination and in the great majority of instances the disease falls within the common period of incubation for other infections. That it occurs rarely is fortunate. It seems reasonable, from the evidence, to presume that vaccinia itself is the cause, even as mumps and measles and typhoid fever may, in rare instances, be the cause of analogous forms of encephalitis.

Even though this assumption still lacks proof, yet in severe types of vaccinia and especially in the nervous disturbances following vaccination, there is ample justification for the employment of the serum of recently vaccinated persons as suggested in England by Sir Thomas Horder and in Holland by Hekman and Paschen.

An available source in this country would be the recent entrants into the training schools for nurses, many of whom are vaccinated upon admission.

It would be cautious for hospitals to prepare small quantities of such serum against the emergency of post-vaccinal encephalitis as is already done against poliomyelitis.

Some of the statistics prepared by the Office Internationale d'Hygiene Publique regarding post-vaccinal encephalitis teach a useful lesson.

During 1929 in Holland 1 case of encephalitis occurred in each 15,000 vaccinations.

Approximately the same proportion occurred in England during 1928 and 1929.

In Holland among the primary vaccinations the proportion was 1 case in 1500 and in re-vaccinated cases it was 1 in 38,000.

There were no cases in 16,000 vaccinations done under 1 year of age. Between the ages of 1 and 2 years 1 case occurred for each 3487 vaccinations, and between 6 and 11 years, 1 case for each 815 vaccinations.

These figures suggest that post-vaccinal encephalitis is essentially a disease following primary vaccination of patients between 6 and 11 years of age.

In Great Britain in 1929 a vaccination order came into force replacing the former four insertions of vaccine by one insertion with a minimum of trauma, and among the 90 British cases reported only 2 had occurred following this procedure.

Another suggestion was that the lymph be diluted with this method. It was found that a sufficient local reaction occurred with a less severe systemic one.

Summary. A case of post-vaccinal encephalomyelitis is recorded, with a report of the postmortem examination of the spinal cord. This shows the histologic features—particularly the area of demyelination—described by Perdrau and by Turnbull and McIntosh.

These features are described and illustrated.

This complication of vaccination has been disturbingly frequent in England and Holland, and some cases are reported from this Continent.

Although a similar histologic picture has been described in other infections it has occurred most commonly following vaccination and there is reasonable ground for assuming that vaccination may be a direct cause of the disease.

The usefulness of immune serum as suggested by Dutch and English writers is brought to notice.

REFERENCES.

- Boyd, William: *Pathology of Internal Diseases*, Phila., Lea & Febiger, 1931.
 Bradford, J. R., and Bashford, E. F.: *Acute Infective Polyneuritis*, *Quart. J. Med.*, 1919, 12, 88.
 Brown, C. L., and Symmers, D.: *Acute Serous Encephalitis*, *Am. J. Dis. Child.*, 1925, 29, 174.
 Collier, J., and Greenfield, J. G.: *The Encephalitis Periaxialis of Schilder*, *Brain*, 1924, 47, 489.
 Donnelly, H. H.: *Vaccinal Encephalomyelitis*, *J. Allergy*, 1931, 2, 396.
 Editorials: *Epidemic Constitution*, *Lancet*, 1928, 2, 233; *The Risks of Vaccination*, *Lancet*, 1931, 1, 85.
 Flexner, S.: *Epidemic (Lethargic) Encephalitis and Allied Conditions*, *J. Am. Med. Assn.*, 1923, 81, 1688.
 Flexner, S.: *Proceedings Assn. Am. Phys.*, 1929.
 Flexner, S.: *Post-vaccinal Encephalitis and Allied Conditions*, *J. Am. Med. Assn.*, 1930, 94, 305.

- Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood, *Arch. Neurol. and Psychiat.*, 1928, **20**, 244.
- Hassin, G. B.: A Note on the Comparative Histopathology of Acute Anterior Poliomyelitis and Epidemic Encephalitis, *Arch. Neurol. and Psychiat.*, 1924, **11**, 28.
- Michels, N. A., and Globus, J. H.: The So-called Small Round-cell Infiltrations (Polioencephalitis and Acute Epidemic Encephalitis), *Arch. Path.*, 1927, **4**, 692.
- Ministry of Health of Great Britain: Report upon Vaccination, November, 1930.
- Musser, J. H., and Hauser, G. H.: Encephalitis as a Complication of Measles, *J. Am. Med. Assn.*, 1928, **90**, 1267.
- Perdrau, J. R.: The Virus of Encephalitis Lethargica, *Brit. J. Exp. Path.*, 1925, **6**, 123.
- Perdrau, J. R.: The Histology of Post-vaccinal Encephalitis, *J. Path. and Bacteriol.*, 1928, **31**, 17.
- Scott, T. F. McNair: Post-vaccinal Encephalitis, *Brit. J. Child. Dis.*, 1930, **27**, 245.
- Sheldon, W. D., Doyle, J. B., and Kernohan, J. W.: Encephalitis Periaxialis Diffusa, *Arch. Neurol. and Psychiat.*, 1929, **21**, 1270.
- Turnbull, H. M., and McIntosh, J.: Encephalomyelitis Following Vaccination, *Brit. J. Exp. Path.*, 1927, **7**, 181.

THE NATURE OF THE HUMAN FACTOR IN INFANTILE PARALYSIS.*

BY GEORGE DRAPER, M.D.,

NEW YORK.

(From the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.)

IF we think of a disease as though it were an entity in itself we shall reach only a partial understanding of its nature. But when we can accept a group of pathologic signs and symptoms within a living organism as the expression of a conflict between its own inherent qualities and those of an equally well identified outside agency, we may view the problem to better advantage. The science of bacteriology has gone far toward establishing the identity and individual characteristics of special microscopic living organisms; and the relationship of some of these to human disease has likewise been established. Indeed, as a result, in certain infectious maladies, the attack and death rates have been almost erased. This consequence, however, has usually come slowly, after painstaking study of the menacing germ. Thus we see the beginning of the control of epidemic cerebrospinal meningitis in Weichselbaum's¹ description of the *Meningococcus intracellularis*.

In 1887 he wrote ". . . in cover glass preparations were found many cocci, usually grouped in pairs placed side by side, and flattened so that each coccus seemed to be a hemisphere. They lay either free between the pus cells or within them. Indeed, they appeared thus in considerable numbers and so reminded one of gonococci."

Then follows a classical statement of the germ's morphology, its

* This work was done under a grant from Mrs. E. Marshall Field.

behavior on various culture media, and its staining reactions. The subsequent history of the growth of knowledge of this diplococcus and its various types is an epic in medicine. For from this simple straightforward description of a specific bacterial morphology, physiology and social group relationships, has come our present understanding of the organism's total individuality and of the disease for which it is in part responsible. Yet notwithstanding all this, we still have not answered the questions why it is possible that so many persons can harbor the virulent meningococcus in the nasopharynx and remain well; and why others at times suffer a septicemia, yet do not develop meningitis. These questions, perhaps, are very like those which we have been asking ourselves about infantile paralysis. Why are so many children taken sick, and so few paralyzed? If the virus is ubiquitous, why is there such a selection of cases? Possibly we have not given sufficient attention to the study of that other essential etiologic factor . . . namely, the human being. If this creature be as necessary to the disease meningitis or poliomyelitis as the diplococcus or the virus, it must be equally specific. It is, therefore, entitled to as much detailed consideration. Furthermore, it is possible to apply to the study of the man very much the same methods of investigation as those employed for the germ. For one can likewise measure and describe his morphology, physiology and psychology, and also his various adjustments to life and environment.

The purpose of this communication is to present a careful description of the human agent of infantile paralysis . . . the child itself; and then to point out certain relationships which this highly specialized constitutional type bears to the phenomena of growth and development.

During the epidemic of infantile paralysis in 1916, it seemed to me that the patients displayed certain definite morphologic characteristics which appeared with insistent regularity. The description then made of these follows:²

"The type of child which seems most susceptible to the disease is the large, well-grown, plump individual who has certain definite characteristics of face and jaws; is broad browed, and broad and round of face. The teeth are particularly interesting. It was noted that in 50 to 60 per cent of all the cases in the hospital at Locust Valley, the central incisor teeth of the upper jaw were separated by a cleft of varying width. The wide-spaced dentition has been a striking feature and frequently involves all the single teeth of both jaws, so that each tooth stands entirely free.

"For many years the close association of this disease with the process of difficult dentition was thought to have some etiologic significance. While no positive proof can be advanced that there is a relationship here, yet it is worthy of note that so many children with poliomyelitis present abnormal dentition.

"Among the adolescents and young adults who acquired poliomyelitis and in whom the disease seemed always to be most severe and, indeed, usually fatal, the type differed from that just described. Instead of the very large, well-nourished individuals with widely spaced teeth, there appeared a more delicately made type. Of the 6 or 8 fatal cases in young adults, seen by the writer, the similarity of appearance of the individuals was so striking that all might have been of one family. All were brunettes, with very delicate dark skins and high coloring of cheeks and lips. Often small, deeply pigmented moles were present on face or neck. There was in every case a definite though finely chiseled maxillary prognathism, and instead of dental separations a tendency to crowding of the teeth. This type was so definitely and so frequently associated with the severe form of the disease that we have come to attach grave prognostic significance to it. In this connection it is interesting to note that a surprising number of the fathers of children ill with poliomyelitis presented striking anthropologic markings. Thus one was a definite acromegalic, while two others were clearly Froelich types, dark-haired, fat faces and bodies, narrow shoulders, broad hips and knock-knees. In three others maxillary prognathism was marked, and although the body stature was small the hands were very large and broad, and there was great physical strength. A seventh father had widely separated upper incisor teeth and was a tall, big-boned individual. Four of the mothers in this group had moderate or marked exophthalmos and were high strung, intensely nervous women. In another instance the mother of two desperately ill cases had an unusual degree of maxillary prognathism.

"Whether or not these facts have a bearing on the question of susceptibility is still problematical. The cited examples, however, are merely a few of the very many similar observations made throughout the summer by the diagnosticians of the New York State Department of Health on Long Island. It is interesting, too, to record the numerous instances of 2, 3, 4 and 5 cases in families with such parental types, suggesting possibly a true family susceptibility."

Although these observations were not followed further in connection with acute anterior poliomyelitis they gave the impulse to investigate, at the Presbyterian Hospital, the general topic of human constitution in relation to disease. The point of view in regard to this matter and the technical methods which have been developed during the intervening years have been applied to cases arising in the epidemic which has just drawn to a close.

Some of the morphologic characters of this group of people which differ from the general population, can be demonstrated by anthropometry and expressed in numerical values. Other features cannot be subjected to mensuration. But observational and descriptive methods suffice to display the striking qualities. Table 1 shows the anthropometric data. It will be seen that the interpupillary space

is unusually wide. This feature is not only emphasized in relation with the upper face (nasion-prosthion) but likewise with the facial diameter, although the latter is also unusually wide. These characteristics, in addition to the somewhat greater distance between the inner canthi, give to the face of these children the broad, wide-eyed expression which was previously noted. In almost all cases there is a definite overbite and frequently a noticeable or pronounced maxillary prognathism. The gonial angle formed by the ascending

TABLE 1.

Anthropometric Data Subjects of Infantile Paralysis

Average Age 9 Years	{	Paralysis Cases	57 Males	52 Females
		Controls	Miscellaneous cases 65 Males	57 Females

	Infantile Paralysis	Averages	Controls
Int. pup. space	♂ 92		♂ 89
nasion prosthion	♀ 97		♀ 90
Int. pup. space	♂ 48		♂ 44
Fac. D	♀ 48		♀ 43
Int. pup. space	♂ 57 mm.		♂ 54 mm.
	♀ 58 mm		♀ 53 mm.
Int. inner canthus	♂ 30 mm		♂ 29 mm
	♀ 31 mm		♀ 29 mm
Hand	♂ 46		♂ 43
	♀ 44		♀ 41
Bill.	♂ 78		♂ 74
Biac.	♀ 77		♀ 75
Gonial angle	♂ 125.3°	>125.3°	♂ 119.2°
	♀ 124.9°		♀ 119.6°
Subcostal angle	♂ 38		♂ 61°
	♀ 38.5°		♀ 57.6°

and horizontal rami is more obtuse in the subject of infantile paralysis than in the members of the control series of miscellaneous diseases. This character is similar to that found in adults of the so-called asthenic variety, as for example, members of the peptic ulcer group who display a rapidly exhaustible energy capacity (adrenal). The narrow subcostal angle is likewise characteristic of these. In this series the inner border of the scapula was not more frequently concave than in the controls. It is interesting to note that, in

paradoxical association with these evidences of the gracile form, the subjects of acute anterior poliomyelitis tend to gain weight and are often definitely pudgy, fat types. The hand index (breadth-length ratio) shows a short, broad form. (Figs. 1 and 2.) This is ordinarily correlated with acromegaloid trends in the facial structure. So far as the rest of the body is concerned, the one outstanding measurable character is the biiliac-biacromal diameter ratio. The pelvis of these individuals is definitely wide as compared with the shoulders. This character is generally accepted as a definite mark of the neuter or feministic type. In both sexes it marks that deficient gonad activity which results in retarded development, and checks metamorphosis toward the finished form of the mature individual of either sex. While this character is usually associated with curving body contours and feminine fat deposits, there are certain individuals afflicted with infantile paralysis who differ. These on the contrary are long, lanky, and often possess exceedingly large long-boned hands. Certain of the young male adults are of this type. As might be expected in the individuals with feminine contours and increased fat, the external genitalia are small; the penis less than average size with pointed glans (Fig. 3). The scrotal sac is short. Several cases of unilateral cryptorchidism appeared, and numerous instances of short spermatic cord which resulted in a partial cryptorchidism on contraction of the cremaster muscles. Before puberty the rotund contours of the male children resemble those of the females. But there are no especially striking physical proportion aspects of the adolescent girls or adult women. Comparatively few of these, however, are stricken.

It is possible to tabulate only some of the characters gained by observation and recorded descriptively. Table 2 shows that the subjects of infantile paralysis possess nail lunulæ much less often than do persons of the control series. Furthermore, their broad, short nails are often deeply imbedded in the surrounding tissues in a manner reminiscent of the nails of acromegaly.

One of the most striking features of the infantile paralysis people is the Mongoloid trend in the palpebral fissure and the not infrequent presence of an epicanthal fold. The latter character, so rarely found in the Caucasian race, appears more often than among the controls (Table 2). But far more common, indeed almost universally so, is the peculiar smooth downward curving slant of the inner half of the arc of the upper eyelid (Figs. 4 to 9). This feature is present whether or not the inner canthus is at a definitely lower level than the outer. The latter arrangement produces the well-defined slant, downward and inward, of the whole eye slit. This feature may often be present in the poliomyelitis people but not by any means in all cases. It is quite distinct from the peculiar flat down-curving arc of the upper lid but may be combined with this. Weninger and Pösch³ have discussed these palpebral fissure designs in respect of

race and show an excellent plate illustrating the various forms. Studies of blood groups recently made by Jungeblut and Smith (unpublished) seem to show that in poliomyelitic children over 5 years of age, 80 per cent fall into Group O1. While there are no reports upon blood groups in Mongoloid idiots, it is interesting to note that Heinbecker and Pauli⁴ found that among pure bred Eskimos 80 to 65 per cent belonged to Group O1. Those Eskimos who showed Groups II, III and IV were half-breeds.

TABLE 2.

Anthroposcopic Data
on
Subjects of Infantile Paralysis

Observations	Infantile Paralysis			Control Group			Infantile Paralysis			Control Group		
	Male						Female					
	Abs.	Pres.	Mark.	Abs.	Pres.	Mark.	Abs.	Pres.	Mark.	Abs.	Pres.	Mark.
Lunulae	80%	16%	36%	40%	40%	20%	1%	27%	2%	45%	46%	9%
Pigmented spots	2%	59.1%	38.7%	41%	50%	9%	93%	53.4%	37.2%	49%	47%	4%
Epicanthal fold	84.2%	15.6%	0%	97%	3%	0%	63%	37%	0%	89%	11%	0%

Of equal importance with the upper lid arrangement is pigmentation of the skin. This is usually present in small, deeply pigmented spots which vary from the size of a pinpoint to 3 or 4 mm. in diameter. As a rule these spots are not raised, although sometimes there are definite moles. They occur most often about the neck, face and upper part of the thorax; but they are also found on the abdomen, back and inner aspects of the thigh. It is worthy of note that in the blond patients these deeply pigmented spots are regularly present in very striking intensity and often in profusion. Furthermore, in addition to the spots, there frequently appear splashes of pale brown, sometimes a definite vitiligo, and often masses of freckles (Figs. 10 and 11).

Another important somatic character of the infantile paralysis children is to be seen in their dentition. Spacing of teeth is commonly found, as well as frequent failures of eruption and all varieties of twisting and irregularity (Fig. 12). Large teeth are seen, perhaps, more often than average size or small ones. The palate vault is usually ample and high and the arch may be either U- or V-shaped.

The skin is smooth and soft and often gives the impression of being stuffed out by the increased subcutaneous deposits. Hypotrichosis of the body is the rule, but in many young children one often sees a surprising degree of fine hypertrichosis of the arms and back. In some of the women there is a marked increase of hair which is distributed in masculine fashion. The nasal eyebrow and general hypertrichosis is sometimes seen in adult males.

In addition to these observations upon certain details of morphol-

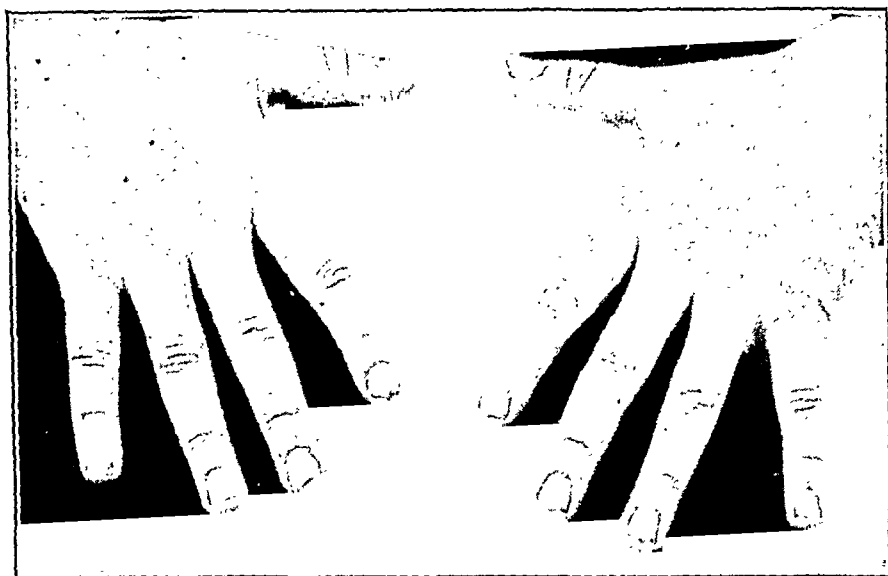


FIG. 1.—Boy, aged 11 years. Hands showing square fingertips and nails without lunulæ.

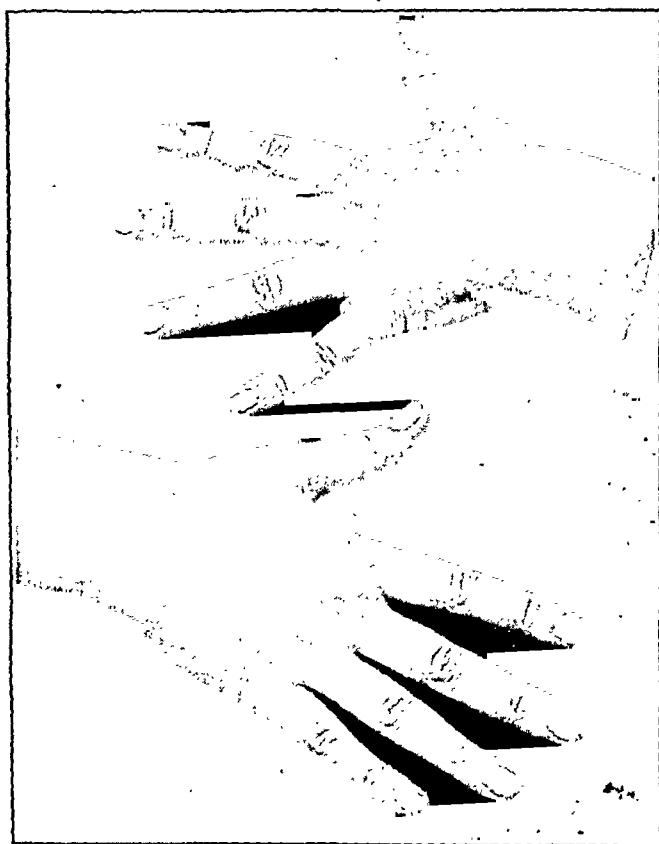


FIG. 2

FIG. 2.—Boy, aged 11 years, showing typical Froelich type hands.

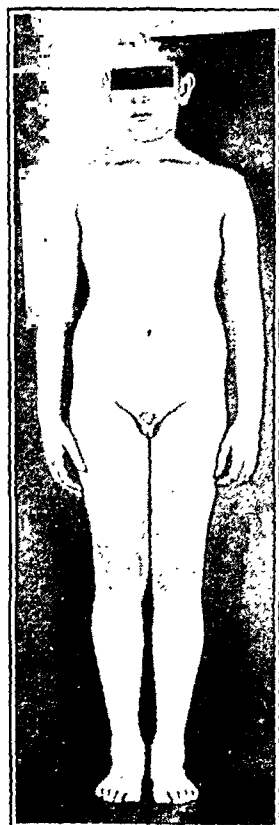


FIG. 3

FIG. 3.—Boy, aged 11 years, showing genital retardation and feministic contours.



FIG. 4.—Girl, aged 13 years, Scotch-English descent, Mongoloid eye.

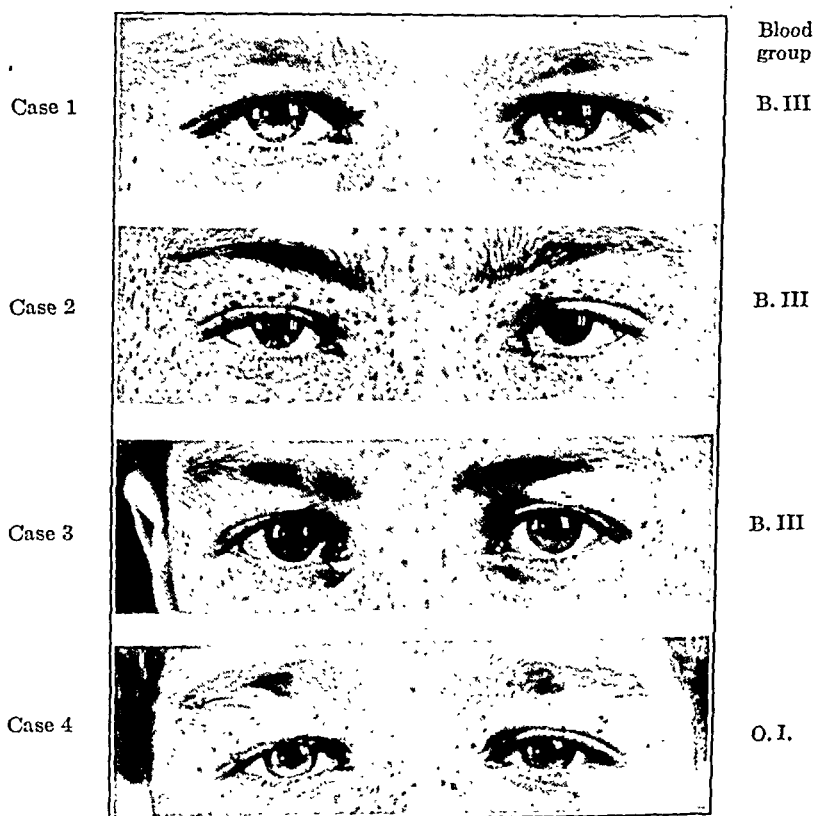


FIG. 5.—Eyes of L. family, brothers, showing varying degrees of Mongoloid slant.
Cases 2, 3 and 4 had the disease. Case 4 paralyzed.



FIG. 6

FIG. 6.—Girl, aged 16 years, showing Mongoloid slant, without epicanthal fold.

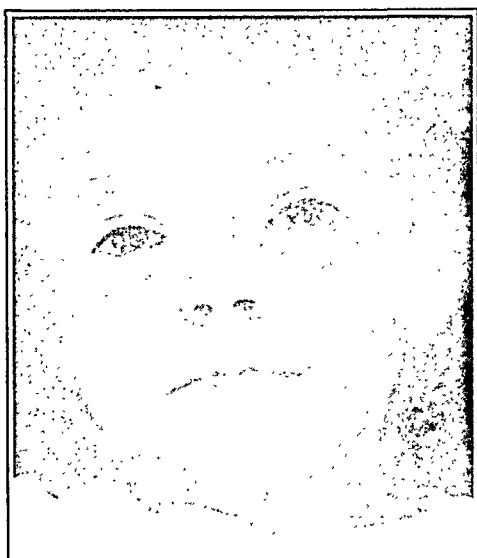


FIG. 7

FIG. 7.—Girl, aged 7 years, showing very wide interpupillary space and Mongoloid slant without epicanthal fold.



FIG. 8

FIG. 8.—Girl, aged 6 years, Mongoloid eye and epicanthal fold. Teeth, show no irregularity.



FIG. 9

FIG. 9.—Boy, aged 7 years, showing Mongoloid eye and epicanthal fold, also spaced teeth. Note also great breadth of face.

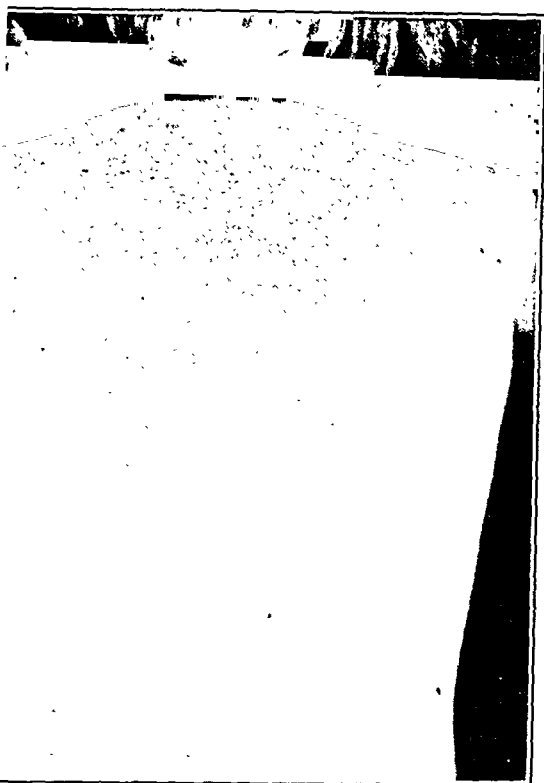


FIG. 10

FIG. 10.—Girl, aged 16 years, blond hair and blue eyes, showing many dark pigment spots and sunburn.

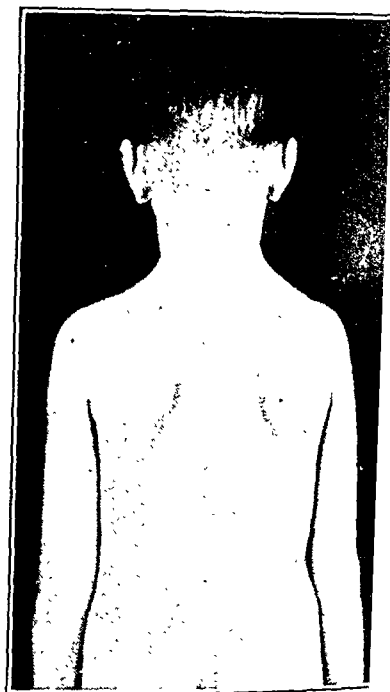
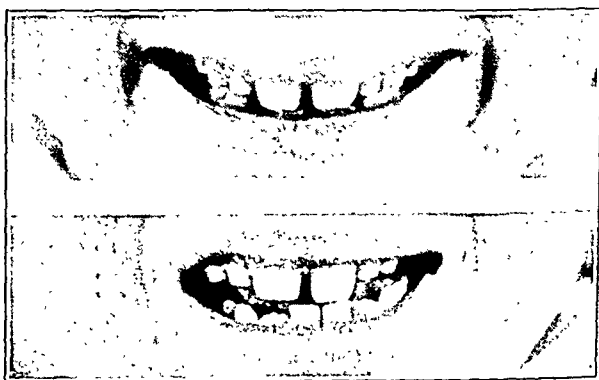


FIG. 11

FIG. 11.—Boy, aged 11 years, Irish. Vitiligo in addition to dark pigment spots.

Case 1



Blood
group

B. III

Case 2

O. I.

FIG. 12.—Teeth of L. family twins. Case 2 paralyzed.

ogy, attention must also be directed toward the general picture which suggests the condition known as lymphatism or status lymphaticus. The delicate skin, long upcurving eyelashes and cherub face in children; the feminine body contours, fine quality hair, and scanty distribution in adults; and the pointed or acorn-shaped glans penis in the men are unmistakable evidence of this type. In this connection it is interesting to recall how frequently the association of status lymphaticus and Addison's disease (adrenal cortex deficiency and pigmentation) has been pointed out.⁵

Thus it appears that the constitutional structure of the infantile paralysis people points toward deficiencies of three glands, namely: pituitary, gonad and adrenal cortex. What the significance of the lymphatism and the Mongoloid trend may be is still unexplained. It is worthy of note, however, that during the recent epidemic there were 3 cases of infantile paralysis in Mongolian idiots at the Willard Parker Hospital. Those⁶ who have studied the latter malformation agree that thyroid deficiency in the mother is an outstanding factor in the genetic background. This is suggestive, in view of the fairly frequent finding of struma, wide eye slits and general nervousness found in many mothers of cases of acute anterior poliomyelitis. So far as the endocrine situation in the individual subject of Mongolism is concerned, attention may be called to Timme's⁷ observations of the anterior portion of the sella turcica in Mongoloid idiots. These are mentioned here because of the recent experiments of Jungeblut and Engle⁸ wherein, under heavy dosage of anterior lobe extract, the undescended testes in monkeys came down rapidly and the animals so treated were likewise protected from lethal doses of poliomyelitis virus. In this connection also the reader is reminded of the clinical observations mentioned earlier in this communication, namely, the occurrence of one-sided cryptorchidism or incompletely descended testes in patients suffering from infantile paralysis.

When all the foregoing observations are considered together, one is reminded of Wade Brown's⁹ observations upon the variation of visceral organ weights in relation to the changing seasons. He showed that the weight of the thyroid of normal rabbits rose from its low point in September to December to a higher level in March. Then it decreased to a low point at the end of May. From there it rose sharply again to a high degree through June, July and August and fell swiftly to the low September point. At the time of the summer thyroid increase the testicular weight falls considerably; the adrenals also decrease, though not so extremely; and the pituitary and pineal increase.

Doubtless these changes represent modifications of normal glandular activity designed to maintain the animal in healthy adjustment with environment during seasonal shifts in climatic and meteorologic conditions. But it is significant that these particular glands are

those which are concerned with the very aspects of growth and development which appear to be unusual in the subjects of infantile paralysis. If the glands themselves are congenitally deficient, or their interaction exceptional, it is reasonable to assume that they may be unable to respond adequately to these seasonal demands.

Conclusion. The highly specialized type of child described above is a causal factor in the occurrence of infantile paralysis, of equal importance with the virus; but so far as the development of paralysis is concerned, the constitution of the child is of greater significance than the virus.

NOTE.—My thanks are due to the Department of Hospitals of New York City, the professional staff of the Willard Parker Hospital, the Hospital for Ruptured and Crippled, the New York Orthopedic Hospital, and the Hospital for Joint Diseases, for their courteous coöperation and assistance in this investigation.

BIBLIOGRAPHY.

1. Weichselbaum, A.: *Fortschr. d. Med.*, 1887, 5, 573.
2. Draper, G.: *Acute Anterior Poliomyelitis*, P. Blakiston's Son & Co., Philadelphia, 1917.
3. Weninger, J. and Pösch, H.: *Mitt. anthropolog. Ges. Wien*, 1924, 54, 267.
4. Heinbecker, P. and Pauli, R. A.: *J. Immunol.*, 1927, 13, 279.
5. Hedinger, E.: *Frankf. Ztschr. f. Path.*, 1907, 1, 527.
6. Bartel, J.: *Status Thymolymphaticus and Status Hypoplasticus*, Leipzig u. Wien, 1912 (Deuticke).
7. Probst, W.: *Beitr. zur Frage nach dem Zusammenhange zwischen Status Lymphaticus und Morbus Addisonii*, Basel, 1909 (Birkhauser).
8. Wiesel, J.: *Lubarsch-Ostertage*, 1912, 15, 416.
9. Gayraud, G.: *Thèse de Paris*, 1928, 16, 9.
10. Halbertsma, T.: *Am. J. Dis. Child.*, 1923, 25, 350.
11. Brousseau, K.: *Mongolism*, Williams & Wilkins Company, Baltimore, 1928.
12. Van der Scheer, Wm.: *Abhandl. aus Neurolog. u. Psychiatr.*, 1927, 41, 1.
13. Timme, Walter: *Arch. Neurol. and Psychiat.*, 1921, 5, 568.
14. Jungeblut, C. W., and Engle, E. T.: Not yet published.
15. Brown, W. H.: *Harvey Lectures, 1928-1929*, Williams & Wilkins Company, Baltimore.

REVIEWS.

PULMONARY TUBERCULOSIS. By MAURICE FISHBERG, Chief of the Tuberculosis Service, Montefiore Hospital, and of its Country Sanatorium for Incipient Tuberculosis. Pp. 1191; 232 illustrations and 8 plates (Two Volumes). Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1932. Price, \$15.00.

THE author has endeavored to depict the advances of the past ten years in knowledge of the pathogenesis, diagnosis, prophylaxis and treatment of pulmonary tuberculosis. Very few pages have been left without critical revision. The chapters of Demography, Pathology and Morbid Anatomy, Roentgenology and Therapeutic Pneumothorax have been completely rewritten, as have the sections dealing with infection, pregnancy, tonsillectomy, sanatorium treatment, intestinal tuberculosis, diabetes and many others. The exceedingly important work on the stages of tuberculosis initiated by the investigations of Ranke have been considered in some detail. New sections have been introduced dealing with the filterable, ultramicroscopic and non-acid-fast types of tubercle bacilli, the etiological rôle of social and economic conditions, infraclavicular infiltrations, the differentiation and prognostic significance of apical as compared with subapical lesions, pulmonary cavities, tuberculous bacillemia, chronic and healed miliary tuberculosis, epituberculous infiltrations, the erythrocyte sedimentation test, the Wassermann test in the tuberculous, B.C.G. in prophylaxis, erythema nodosum, heliotherapy in pulmonary, intestinal and laryngeal tuberculosis, syphilis, asthma and hay fever in the tuberculous, the Gerson salt-free diet, insulin in tuberculous diabetics, chemotherapy, especially sanocrysin, the eugenic aspects of tuberculosis, etc. The medical phases of the operative treatment of pulmonary tuberculosis, phrenicectomy, apicolysis, extrapleural thoracoplasty, oleothorax, etc., have been considered in new chapters. Over one hundred new illustrations, mainly roentgenograms, have been added.—(*From the Preface.*)

TYPHOID FEVER. By WILLIAM BUDD, M.D., F.R.S. Pp. 184; 5 illustrations; 1 in color. New York: American Public Health Association for Delta Omega, 1931. Price, \$5.00.

FROM a preliminary notice the reader learns that the Delta Omega Society intends to republish a series of public health classics (of which this is the first) as a contribution to the cultural background of public health. The book is "published on subscription" by the American Public Health Association, though no name of publisher appears on the title page. Except for the short untitled statement above referred to, a title page dated "New York 1931," the correction of 3 errata, and 2 changes in illustration, the book is an untouched reprint of Budd's original essay, written in 1874. It appears in a well prepared, numbered and limited edition, with good paper, attractive type and a stout cardboard protecting box.

The text forms an interesting and highly important link in the chain of typhoid history, though it is questionable whether it should be called the "epoch making work," stated in the advertisement. Written before the advent of the typhoid bacillus, but years after the disease had been clearly

differentiated from typhus, nosologically and pathologically, it promotes the correct, but then apparently not generally accepted thesis that typhoid is a "contagious or self-propagating disease" in which "the specific poison" is bred in the sick patient and "cast off chiefly in the discharges of the diseased intestine." Budd believed, however, that persons could take the fever either from contaminated water or infected air. The immunity conferred by a previous attack is clearly recognized. "By destroying the infective power of the intestinal discharges by strong chemicals or otherwise, the spread of the fever may be entirely prevented . . . the disease may in time be finally extinguished." An appendix details the steps to be taken to disinfect the excreta and bed linen of the patient and the hands of those in contact with him. Except for the typhoid carrier, not recognized for another generation, the recommendations would be considered adequate today. It is to be hoped that this reprint will retrieve for the author the credit that his work merits.

E. K.

MODERN PROCTOLOGY. By MARION C. PRUITT, M.D., L.R.C.P., S. (Ed.), F.R.C.S. (Ed.), F.A.C.S., Associate in Surgery, Emory University School of Medicine, Atlanta. Pp. 440; 233 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$8.00.

THIS book is intended to offer the profession a concise summary of the modern methods of examination and treatment of anal and rectal diseases. It begins with the usual chapters on anatomy and physiology, fairly well illustrated with drawings mostly taken from standard works on anatomy. A chapter on anesthesia unnecessarily includes sections on the technique of administering chloroform, ether, etc. It merely mentions local anesthesia for anal operations, but gives more space to caudal, sacral and subarachnoid block. The various rectal diseases are discussed systematically, presenting a description of the disease, its incidence, etiology and methods of treatment. As a rule the author describes several alternative methods of therapy, often without indicating his own preference.

The injection treatment of hemorrhoids is well presented, giving more data concerning the contraindications and complications than is usual. The sections on the minor surgical diseases of the anus are very well presented. The author describes the conservative and the more radical methods of therapy, pointing out the advantages and disadvantages of each method.

The author devotes considerable space to the treatment of rectal prolapse, but usually does not give the reader any indication as to the efficacy of the methods which are presented. A comparatively small portion of the book is devoted to tumors of the rectum and anus. The Broders' classification and grading of rectal tumors is accepted without modification. The technique of the operations for the excision of rectal tumors is so briefly described that this part of the work is of little value as a reference, either to the experienced surgeon or to the inexperienced student. The same criticism may be made of the section on radiation therapy, in which no reference is made to the work being done along this line at the Memorial Hospital, New York.

The work of Bargen on ulcerative colitis is only briefly mentioned. The author commends appendicostomy in the treatment of the severer forms of this disease, but has obtained the best results from autogenous vaccines in the milder cases.

The book impresses the reader as an attempt to make a résumé of the literature on anal and rectal diseases, rather than a work which is the result of the author's observations and experience. The illustrations are only fair and one obtains the impression that a large part of them are not original.

The book will probably be of value to the general practitioner, as a fairly comprehensive summary of modern proctology, but can hardly be considered as a reference work to be used by the surgical specialist. L. F.

TABLES OF FOOD VALUES. By ALICE V. BRADLEY, B.S., Supervisor and Instructor of Nutrition and Health Education, State Teachers College, Santa Barbara, Calif. Peoria, Illinois: The Manual Arts Press. Price, \$2.00.

THIS book, as its name implies, is entirely a reference work. The text consists of a general discussion of the rôle of the food elements in the body and an explanation of the use of the tables.

It is made up of tables of foods grouped together according to their character. Besides the customary carbohydrate, protein and fat and total caloric values, there are given the calcium, phosphorus and iron content where known. On the opposite page is a continuation of the chart in which the same foods are listed, showing their value as a source of the same minerals, of vitamins (listed separately), and their bulk. By employing the letter X to denote a small amount and XXXXX a very large amount of any factor, it has been possible to compile a group of charts from which, at a quick glance, the reader can choose the foods containing certain desired qualities without detailed study of the figures. The reaction, either acid or basic, where known, is also included.

Part I gives the food values of average servings by household measures with the equivalent weight in grams. In Part II the same tables are repeated with the 100 gm. portions of the food and the equivalent of these 100 gm. portions in household measures. In these latter tables all figures read as grams or per cent.

A valuable addition to the book is the inclusion of the recipes which have been used in compiling the values of the various mixed foods, such as beverages, breadstuffs, desserts, cakes, etc. The sources of the material comprising the tables are such as to establish confidence in their accuracy.

The book is pleasing in appearance and is of a convenient size for easy handling. The tables are so arranged as to be easily read. "Tables of Food Values" will be a valuable aid to physicians and dietitians; in fact, to anyone who is interested in the problems of nutrition. R. R.

SIMPLIFIED DIABETIC MANAGEMENT. By DR. JOSEPH T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., Chief of Diabetic Clinic and Associate Visiting Physician, Presbyterian Hospital in Philadelphia, and DR. HERBERT T. KELLY, M.D., A.A.C.P., Associate in Diabetic Clinic, Presbyterian Hospital in Philadelphia. Pp. 191; 7 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$1.50.

THIS book is one more of the line of diabetic manuals which have made their appearance at intervals during a number of years. The authors have undertaken the all but impossible task of writing for both patient and physician. While in so doing they have covered much ground helpful to the patient, there is danger to the diabetic in a little medical knowledge gained in this way which may tend to make him feel independent of his physician and lead him into difficulty. Such information as the necessity for electrocardiographic tracings, pre-operative care, and choice of anesthetic are certainly subjects regarding which the patient should not be taught to use his own judgment.

The diet instruction is simple and clear, and as the figuring of both percentage and unit methods is explained, patients should have no difficulty in their use. Instructions for the patient in emergency treatment, food tables and sample diets complete the contents.

R. R.

PATHOLOGY, BACTERIOLOGY AND APPLIED IMMUNOLOGY FOR NURSES. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital. Pp. 324; 112 illustrations. Milwaukee: Bruce Publishing Company, 1931. Price, \$2.50.

This book intended for a text could be used to better advantage as a reference.

Pathology precedes bacteriology whereas actually in the course of study it follows sometime later. The beginning student would surely be overawed by the material included in pathology she would have to wade through to find bacteriology. The subject matter of pathology seems contrary to the intention of the author to "more nearly approximate what the practice of medicine necessitates than what the practice of nursing requires."

The laboratory exercises in bacteriology would be more useful if they followed the text material they were supposed to illustrate.

There are chapters on "The Nurse and the Education of the Public" and "vivisection and antivivisection" that alone would make the book a valuable addition to the library of every school for nurses.

M. S.

DIAGNOSIS IN JOINT DISEASE. By NATHANIEL ALLISON, M.D., F.A.C.S., Professor of Surgery, in Charge of Division of Orthopedic Surgery, University of Chicago, and RALPH K. GHORMLEY, M.D., Associate in Orthopedic Surgery, Mayo Clinic. Pp. 196; 251 illustrations, 11 in color. New York: William Wood & Co., 1931. Price, \$9.00.

THE authors have collected the results of their complete study of 289 cases of arthritis and have analyzed them in an effort to increase the accuracy in diagnosing joint diseases. Their study includes the clinical radiologic, bacteriologic, chemical and pathologic findings, and their analysis is based on the answer to three fundamental questions. I. What is the etiologic factor? II. What tissue of the joint is primarily affected? III. What is the character of the tissue change?

The introductory chapter, giving a résumé of the physiology and chemistry of joint structures, is followed by one in which the authors present their own classification of arthritis. They divide joint diseases into those of known and those of unknown origin. The four main subdivisions of known origin are traumatic arthritis, bacterial arthritis, arthropathies and arthritis due to constitutional disease. Those of unknown origin are proliferative arthritis, degenerative arthritis, and the unclassified arthritides. This "simple and workable classification" has been based upon the pathology and etiology of the various diseases. The authors are confident that an understanding of the facts of the etiology and pathology will lead to an early diagnosis and the use of better diagnostic terms in joint disease.

The excellent chapter on tuberculosis discusses the pathologic changes in the synovia, cartilage and bone, and is illustrated by photomicrographs, many of them in color.

The next chapter on traumatic arthritis and "loose body" formation discusses the pathology of joint trauma, and the numerous theories as to the etiologic factor in osteochondritis dissecans.

In the chapter on pyogenic infection of joints, the authors point out that the inflammatory processes in a joint produced the same chain of histologic pictures and that the various classifications, serous, seropurulent and purulent, are only stages in the process. They have studied many types of joint infections and describe the changes to be found in the synovia, cartilage and bone. The rheumatic type of joint infection is not discussed because of the lack of material.

In the discussion of arthritis of uncertain origin the authors point out the clinical characteristics, physical signs, Roentgen ray, and bacteriologic findings. The pathologic studies, however, are those which show the most typical and characteristic changes. In the proliferative type they have noted changes similar to those observed by Nichols and Richardson, a proliferation of the synovia, of the connective tissue elements in the marrow and secondarily a transformation of the connective tissue into cartilage or bone.

One new pathologic finding has been observed by the authors which is characteristic of the proliferative arthritis, *viz.*, focal collections of lymphocytes in the synovial membrane. These changes are well illustrated by colored microphotographs.

Under the term degenerative arthritis are described the joint changes which have been discussed by various authors under the names of arthritis deformans, osteoarthritis, hypotrophic arthritis, etc. They have confirmed pathologic findings as described by Nichols and Richardson.

At the end of each chapter are given a series of case reports illustrated by typical Roentgen rays and microphotographs, in which are described the outstanding symptoms, the clinical notes and a report of the gross and microscopic pathology. No suggestions are given as to the treatment of any of the diseases which are discussed. The volume presents an outstanding contribution to the profession on the subject of diagnosis in joint diseases. It is simply written, beautifully bound and illustrated and should prove an invaluable aid not only in the library of the surgeon and orthopedist but also as a reference for the internist and the pathologist.

L. F.

BOOKS RECEIVED.

NEW BOOKS.

Transactions of the American Otological Society, Inc. Sixty-fourth Annual Meeting, Briarcliff Lodge Hotel, Briarcliff Manor, N. Y., June 18 and 19, 1931, Vol. XXI. Pp. 316; illustrated. Published by the Society.

Control of Conception. By ROBERT LATOU DICKINSON and LOUISE STEVENS BRYANT. Pp. 290; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.50.

Psyllium Seed: The Latest Laxative. By DR. J. F. MONTAGUE, Medical Director, Montague Hospital for Intestinal Ailments, etc. Pp. 170; 20 illustrations. New York: Montague Hospital for Intestinal Ailments, 1932.

Medical Aspects of Old Age. By SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, etc. Pp. 205; 7 illustrations. New York: Macmillan & Co., Lt., 1932. Price, 7/6.

Pathology for Nurses. By EUGENE C. PIETTE, M.D., Pathologist and Director of the Clinical Laboratories of the West Suburban Hospital, Oak Park, Illinois, etc. Pp. 251; 65 illustrations, some in color. Philadelphia: F. A. Davis Company, 1932. Price, \$1.75.

- Laboratory Technique.* By R. B. H. GRADWOHL, M.D., Director, Gradwohl School of Laboratory Technique, etc. Pp. 462; 148 illustrations. St. Louis: Gradwohl School of Laboratory Technique, 1932. Price, \$8.00.
- Papers on Surgery and Other Subjects.* By GEORGE TULLY VAUGHAN, M.D., LL.D., F.A.C.S., Professor Chief of Surgery, Georgetown University; Chief Surgeon Georgetown University, etc. Pp. 408; illustrated. Washington: W. F. Roberts Company, 1932.
- Reflex Activity of the Spinal Cord.* By R. S. CREED, D. DENNY-BROWN, J. C. ECCLES, E. G. T. LIDDELL and C. S. SHERRINGTON. Pp. 183; 71 illustrations. New York: Oxford University Press, 1932. Price, \$3.25.
- The House that Freud Built.* By JOSEPH JASTROW, PH.D., LL.D. Pp. 293, New York: Greenberg, 1932.
- Human Sterilization.* By J. H. LANDMAN, PH.D., J.D., J.S.D., The College of the City of New York. Pp. 341; illustrated with figures and tables. New York: The Macmillan Company, 1932. Price, \$4.00.
- Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis.* Monograph Series No. 55. Pp. 219; illustrated. New York: Nervous and Mental Disease Publishing Company, 1932. Price, \$4.00.
- The Medical Clinics of North America, Volume 15, No. 4 (Boston Number, January, 1932).* Pp. 268; 18 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- The Medical Clinics of North America, Volume 15, No. 5 (New York Number, March, 1932).* Pp. 340; 61 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- The Medical Clinics of North America, Volume 15, No. 6 (Mayo Clinic Number, May, 1932), Index Number.* Pp. 239; 31 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- The Surgical Clinics of North America, Volume 12, No. 1 (Chicago Number, February, 1932).* Pp. 240; 92 illustrations. Philadelphia: W. B. Saunders Company, 1932. Paper, \$12.00; Cloth, \$16.00.
- The Surgical Clinics of North America, Volume 12, No. 2 (New York Number, April, 1932).* Pp. 307; 82 illustrations. Philadelphia: W. B. Saunders Company, 1932.

NEW EDITIONS.

- Pulmonary Tuberculosis.* Two volumes. By MAURICE FISHBERG, Chief of the Tuberculosis Service, Montefiore Hospital, and of its Country Sanatorium for Incipient Tuberculosis. Pp. 1191; 232 illustrations, and 8 plates. Fourth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1932. Price, \$15.00.
- Modern-General Anesthesia.* By JAMES G. POE, M.D., Lecturer on General Anesthesia in the Medical and Dental Departments of Baylor University, etc. Pp. 231; 12 illustrations. Second edition, completely revised and enlarged. Philadelphia: F. A. Davis Company, 1932. Price, \$2.50.
- Theoretical discussions having been omitted this edition has included recent advances without loss of brevity.
- Text-book of Massage.* By L. L. DESPARD, Member Chartered Society of Massage and Medical Gymnastics. With 2 chapters contributed by HESTER S. ANGOVE, Member Chartered Society of Massage and Medical Gymnastics, etc. Pp. 474; 222 illustrations. Third edition. New York: Oxford University Press, 1932. Price, \$6.00.
- This edition maintains the general excellent appearance of Oxford Press publications. The latter half of the book presents the principles of massage in a satisfactory manner; the former half, a treatise on anatomy and physiology, were better omitted with an appropriate reduction in price.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Plasma Proteins in Relation to Blood Hydration. VIII.—*Serum Proteins in Heart Disease.*—The increasing importance of the protein content of the blood serum as a factor in the production of edema has been brought about largely through the biochemic studies of numerous investigators, especially Peters and his coworkers. The original concept of Starling, advanced 37 years ago, is that capillary blood pressure which has a hydrostatic force tending to drive out fluid from the vessels and that the osmotic pressure of the blood colloids, principally serum protein which tends to draw fluid from the tissues into the blood stream, are responsible for the to and fro passage of fluid from the blood and the tissue spaces. Alteration in this physiologic arrangement, notably whereby the serum proteins, especially serum albumin, diminish, is responsible for the production of edema in a certain number of disorders. Outstanding examples of such edema occur in nephrosis and in starvation. In heart failure the chief cause of the associated edema is the result of the increase of capillary pressure from the associated venous stasis. The rôle of the serum proteins in the production of edema in congestive failure is apparently somewhat limited. PAYNE and PETERS (*J. Clin. Invest.*, 1932, 11, 103) have studied a series of patients with heart failure from the point of view of the serum proteins. They note, first, the various factors which may alter considerably the protein content of the serum in heart disease, factors such as albuminuria, hydremia, filtration of protein through the capillary walls, and malnutrition. None of these apparently, except the last, plays a very important part in the hypo-albuminemia. For example, the loss of albumin in the pleural effusion is comparatively slight, even an enormous effusion taking from the blood serum only 60 gm. of protein. The important factor in the reduction of protein content of the blood seems to be malnutrition. The patients that exhibit a good state of nourishment have high serum protein, while those with low proteins

are distinctly undernourished. Malnutrition seems to exert its effects largely on the albumin fraction of the serum protein. The correlation of the observations made by the authors are most consistent and seem definite proof that serum albumin deficits in heart failure are the result of malnutrition. Edema may occur at any time if the capillary blood pressure rises considerably, irrespective of the protein value of the serum. Its production, write Payne and Peters, can proceed only to the point where the mean capillary pressure equals the oncotic pressure. The reduction of the latter through serum protein deficiency, given an equal degree of venous congestion, will occasion considerable increase in the edema. It is consistent with the main thesis, that edema should be found usually in patients with low serum protein, which in turn depends upon the albumin deficit from the malnutrition. Aside from the most interesting and instructive studies of disturbed physiology, the practical bearing of these studies on the treatment of the cardiac is obvious. It is a mistake to restrict diet, and more particularly the protein, when heart failure exists. The usual causes of loss of weight and malnutrition in cardiac disease, namely, anorexia and nausea and vomiting, may be overcome by the selection of proper foods, so that a diet which contains not only liberal quantities of protein but also sufficient caloric value can be arranged through selectivity of food to give to the heart patient not only sufficient proper food but the type of food which will not overtax the digestive apparatus. Feeding properly the patient with congestive failure will apparently help considerably in combating edema, one of the important expressions of heart failure. Such a patient should be treated as one who has a wasting condition with adequate, complete diets containing ample quantities of protein. Only when it is necessary on account of digestive disturbances should the diet be restricted and then only for a short time.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Cancer of the Rectum and Rectosigmoid.—COFFEY (*Am. J. Surg.*, 1931, 14, 1611) states that cancer of the rectum and rectosigmoid constitutes approximately 12 per cent of all the cancers that affect the human body. Cancer of the rectum and rectosigmoid, because of its anatomic location and the accessibility of its lymphatics is one of the most curable of cancers. The operability as cases come to the intestinal surgeon is approximately 50 per cent. Of the operable 50 per cent, approximately 50 per cent are susceptible of 5-year cures. The author is unequivocally committed to the multiple-stage operation as a routine procedure with only rare exceptions. Because of the almost uniformly good results in cases coming for operation after a preliminary colostomy has been performed elsewhere as an emergency operation, as well as in his own practice and because such amazing results have been reported by Prof. Grey Turner and others as to the difference between the mul-

multiple-stage operation and the one-stage resection operation for cancer of the colon, the author has become firmly convinced that the two-stage radical operation should be preceded some weeks before by a simple colostomy in all cases of rectosigmoid cancer.

Fractures of the Femur. Treatment by the Russell Method of Traction.—LUND (*Arch. Surg.*, 1931, 23, 889) states that he has obtained the best results in cases of fracture of the femur by the use of the Russell traction apparatus. This method depends on a natural comfortable position of the limb with a minimum of weight whereby the equilibrium of the muscle is restored. With this restoration of muscle tone and position, the fractured ends of the bone will fall into a more or less natural alignment provided there is no interposed tissue. One must bear in mind that an absolute restoration of anatomic position is not necessary for a good functional result. The essayist has used the method as described by Russell with practically no change. The apparatus, its application and the after care of the patient have been described. The results have been analyzed and the following deductions drawn. The Russell method of traction is the method of choice in treating all types of fracture of the femur from the intertrochanteric to the lower epiphyseal regions. It gives satisfactory position and alignment in all cases except when muscle is interposed between the fractured ends. It gives a maximum of permanent changes in the joint as compared with other methods. The average period of traction in fractures of the femur is 9 weeks, of hospitalization 12 weeks and of temporary disability 9 months. The method is inexpensive, easy to apply, comfortable to the patient and materially simplifies nursing care.

Diagnostic and Therapeutic Injections of the Sympathetic Nerves.—FLOTHOW (*Am. J. Surg.*, 1931, 14, 591) claims that the most satisfactory diagnostic procedure for conditions affected by the sympathetic nervous system is the direct injection of procain at the sympathetic nerves; by means of these diagnostic injections it is possible to determine accurately whether or not therapeutic measures should be directed toward the sympathetic nervous system. The two factors most frequently involved are pain and diminished blood supply. Diagnostic injection gives definite information as to relief of pain and what quantitative increase in vascularity may be obtained by therapeutic measures. Alcohol injection of the sympathetic nerves is an established therapeutic measure which has been used successfully in arteriosclerotic conditions, Buerger's disease, Raynaud's disease, chronic polyarthritis, trifacial neuralgia, atypical facial pains, angina pectoris, trophic ulcers, neurotrophic skin lesions, diabetic neuritis and other conditions. Alcoholic injection does not have the permanency of the operation and is therefore not indicated where permanent maximum blood supply is essential except where operation is definitely contraindicated.

Operative Treatment of Abscess of the Lung.—LILENTHAL (*Surg., Gyn. and Obst.*, 1931, 53, 788) says that the principles of the operations for lung abscess are always the same. The head of the patient should be lower than his hips. Local anesthesia should be used, if possible; if not some extremely light form of so-called analgesia should be used

so that the cough reflex may not be abolished and the danger of aspiration into the opposite lung may be reduced. Heavy narcotic dosage and anesthesia by avertin or other drugs should be avoided. Evacuation should be by the most direct route, avoiding free pleural involvement. The drainage opening should be well above the lower limit of the abscess. Manipulation of the cavity should be gentle, so as to prevent dangerous hemorrhage. One should refrain from the natural surgical tendency to simplify multiple abscess cavities at the time of operation. The packings should never be so firm as to dislocate the mediastinum. Whenever adhesions are feared rubber dam should be employed as a packing. The wound pattern makes comparatively little difference, but an opening which promises to enter the abscess by the most direct route should be employed with such preliminary or additional incisions as may be necessary for perfect exposure. As a rule chest wall flaps should not be employed, even though they apparently permit of drainage at the lowest point, because frequent dressings will be necessary and the flap impedes complete exposure.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

The Beneficial Influence of Diet on Hyperthyroidism.—The rôle of diet in the treatment of hyperthyroidism has been emphasized repeatedly. Earlier attempts to influence the course of the disease with a high protein and caloric diet generally failed. KOMMERELL (*Deutsch. Arch. f. klin. Med.*, 1931, 171, 205) now claims that a diet low in protein and high in carbohydrate is beneficial. The patient is placed for 14 days on a normal "house" diet. During this period control observations are made of the basal metabolism and general condition. Following this period the patient receives a diet containing about 500 calories. The diet is then gradually increased within 3 or 4 days to the caloric requirement of the body at rest. The diet is specially rich in fruits. A typical diet might be—first day: 40 gm. of flour, 30 gm. of bread, 400 gm. of fruit, 10 gm. of butter, equalling 530 calories; second day: 75 gm. of flour, 100 gm. of bread, 600 gm. of fruit, 20 gm. of butter, equalling 990 calories; third day: 20 gm. of flour, 60 gm. of noodles, 150 gm. of bread, 500 gm. of fruit, 300 gm. of vegetables, 50 gm. of butter, equalling 1330 calories; fourth day: 50 gm. of glucose, 70 gm. of flour, 150 gm. of bread, 3 gm. of egg yolk, 50 gm. of cream, 200 gm. of vegetables, 100 gm. tomato, 600 gm. of fruit, equalling 1840 calories; fifth day: 100 gm. of glucose, 70 gm. of flour, 150 gm. of bread, 500 gm. of potatoes, 125 gm. of "Yoghurt" milk, 100 gm. milk, 50 gm.

of butter, 200 gm. of vegetables, 800 gm. of fruit, equalling 2400 daily calories. This diet is then continued. The 24 cases treated suffered from true 'Morbus Basedowii' and not from toxic adenoma. Only 3 of the patients had a basal metabolism below 50 per cent. Frequent, occasionally daily, measurements of the basal metabolism were performed. Only 6 cases showed no improvement, and 3 cases no marked improvement. The other cases, according to the author, showed distinct improvement. The age of the patient and the duration of the disease did not seem to influence the efficiency of the diet. In severe cases of thyrotoxicosis it would be advisable to use the diet no longer than three weeks, as a preparation for operation, since the basal metabolic rate reaches its minimum within this period, usually lowering at a rate of 15 to 20 per cent. The author suggests that the diet may change the sensitivity of tissues to the thyroid hormone. He considers the diet only a support to other therapeutic measures.

The Rôle of the Anterior Pituitary Gland in the Etiology and Treatment of Cancer.—The anterior lobe of the pituitary gland plays an important rôle in promoting growth. Zondek found that in 15 per cent of 118 cases of malignant disease the anterior pituitary hormone was present in the urine in sufficient quantity to give a positive Zondek-Aschheim reaction. Evidence is available that extract of the posterior lobe is capable of retarding growth. SUSMAN (*Brit. Med. J.*, 1931, p. 795) examined the histology of the anterior and posterior pituitary lobes in normal and diseased individuals and on a basis of his observations claims that in cancer there is probably an imbalance between the ductless glands which permits the development of the new growth. There is frequently an overactivity of the anterior pituitary, an underactivity of the posterior pituitary and an enlargement of the islets of Langerhans. These findings were then subjected to experimental tests. One hundred mice "painted with shale oil five times a week" were used. The incidence of epithelioma indicates that an abundant supply of glucose promotes epithelioma in mice. One group of mice with epithelioma received 0.1 to 0.3 cc. of pituitrin subcutaneously twice a day. Within 3 days the growth had contracted considerably. In from a month to 6 weeks the growth often separated, leaving a simple ulcer. Four patients with cancer of the tongue, cheek and breast were then placed on a diet low in carbohydrate and received 0.5 to 2 cc. of pituitrin twice daily. During the 6 weeks' period of treatment, the authors claim, there was regression in the growth; but this regression came to a standstill. For this reason, and in order to restrain the influence on the anterior pituitary, an ovarian extract (theolin) in amounts of 0.2 cc., was added to the therapy. The amounts of theolin was varied from 0.25 to 0.5 cc. once or twice daily. Five patients were treated in this manner. In 4 cases the tumors showed regression, the patients felt better, life has been prolonged. In the fifth case, with a slow-growing epithelioma of the dorsum of the foot, the tumor became smaller and at the end of the 7 weeks was enucleated with "a blunt instrument."

[EDITOR'S NOTE.—Although this communication should be considered only as preliminary and suggestive, it is of distinct interest, as scattered reports have recently become available indicating that certain internal secretory products are capable of influencing the growth of certain types of cancer.]

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Schilling Hemogram: Its Application in Pediatrics.—NUSSBAUM (*Arch. Pediat.*, 1932, 49, 201) says that the application of the Schilling method of study of the blood is a valuable aid in the establishment of the presence of infection in pediatric cases. He presents a study of 232 pediatric cases with 432 hemograms. He found that the chief changes in the hemogram in the presence of active infection were the increase of the percentage of immature neutrophilic granulocytes in the peripheral circulation which is termed regenerative shift, the toxic degenerative changes in the neutrophilic granulocytes represented by purplish staining granules, a decrease in percentage of lymphocytes and disappearance of the eosinophils from the peripheral circulation. According to the percentage of immature granulocytes, such as stab, juveniles, myelocytes and myeloblasts, present in the peripheral circulation, the cases are grouped into five classes: No regenerative shift in less than 10 per cent; mild regenerative shift in from 10 to 20 per cent; moderate regenerative shift in from 20 to 35 per cent; marked regenerative shift above 35 per cent; marked regenerative shift with signs of exhaustion of the bone marrow, when more than 10 per cent of myeloblasts, myelocytes and juveniles are present. The degree of regenerative shift is proportional to the virulence of the invading organism with slight individual variations. The hemogram can be utilized as an aid in making a prognosis. Periodic study of the blood during the active stage of infection will indicate progress of the infection and aid in deciding the prognostic statement. Common ailments were studied and characteristic changes were found in each. The blood changes during and after the administration of nirvanol in chorea cases was studied also. The presence of leukocytosis and eosinophilia indicated an allergic factor in the reaction following this medication. The leukocytosis and moderate regenerative shift indicated either that the nirvanol was capable of direct stimulation of the bone marrow or acted indirectly by activating the organism associated with chorea. Sixty-five contagious diseases were studied, and characteristic hemograms were found in each. The use of the hemogram as a criterion for the administration of scarlet fever antitoxin and as an aid in deciding further use of serum in meningococcal meningitis is projected as the basis of a study to be made later. It is pointed out that the Schilling hemogram does not make a diagnosis, but is useful as an aid to the clinical bedside observations and other laboratory data. It has been found to be far superior to the old method of differential count, especially in the presence of infection.

The Respiratory Metabolism in Infancy and Childhood: The Calorigenic Action of Thyroid Extracts in Normal Infants.—WYATT, WEYMULLER, LEVINE and KELLY (*Am. J. Dis. Child.*, 1932, 43, 845) found that the thyroid extracts in adequate dosage exert a calorific action in infants with apparently normal thyroid glands and often induce in these subjects clinical symptoms characteristic of spontaneous hyperthyroidism. The metabolic response of these subjects to thyroid

extracts in smaller dosage is inconstant. The minimal amounts of the drug capable of producing profound clinical and metabolic reactions in infants without hypothyroidism are apparently comparable to the dosage required to induce a similar reaction in adults without hyperthyroidism. They exceed notably the usual dosage effective in subjects of all ages with hyperthyroidism. The usual persistence of thyroid action in these normal infants was approximately 2 to 3 weeks. This time interval coincided with the usual duration of thyroid action reported for normal adults, and is considerably shorter than the persistence of such action in subjects with hypothyroidism. In terms of absolute dosage the whole gland product and the desiccated extract vary markedly in their potency as calorogenic agents, but they are equally potent as judged from their iodine content. On the latter basis, thyroxine, the active principle of the thyroid hormone, appears to be the most potent calorigenically of the three types of product. The iodine content would seem to be the best single criterion of the potency of the products and it is recommended that only thyroid preparations of known iodine content be used as therapeutic agents.

The Present Status of the Treatment of Hirschsprung's Disease.—RANKIN and LEARMONTH (*Am. J. Surg.*, 1932, 15, 219) present studies of 8 cases of Hirschsprung's disease in which offensive measures were directed against the autonomic nervous system. These cases lend belief to the hypothesis that the condition is sometimes undoubtedly of neurogenic origin. Physiologic basis for sympathetic neurectomy in congenital megacolon lies in the theory that the interruption of these sympathetic nerves deprive the bowel of the "brake" on its activity, and that the tonus of the internal sphincter is at the same time diminished permitting the bowel to rid itself of its content. The sympathetic nerves are "filling" nerves, their preponderant action diminishing intestinal contractility and allowing it in a more or less quiescent state to accumulate its content. Section of these nerves is directed toward the essential pathologic characteristic of the lesion, dilatation and hypertrophy. The former condition permits accumulation of intestinal content and the latter is the result of some type of obstruction. Although the etiology of this condition is somewhat uncertain, the disease may still be attacked by relieving the three principal anatomic features and attempting to diminish the dilatation of the colon, to overcome the excessive control by motor nerves and to relieve any opposition to expulsion of the content offered by the internal sphincter. The accomplishment of the first two considerations is brought about by division of the inferior mesenteric nerves and the third by division of the presacral nerves. This particular type of operation accomplishes these results as evidenced not only by the 8 cases comprising this report, but also by numerous other cases in the literature. At the same time it does not endanger the function of any viscera by interruption of important efferent or afferent fibers. The mechanism for defecation is not affected by division of the inferior mesenteric nerves. In the 8 cases reported function was returned, tardily in some, but nevertheless neurectomy exerted a direct influence and in all the obstipation and dilatation were overcome in varying degree. The safety of the operation and the desirability of its application in well-selected cases are established.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Irradiation Therapy in Functional Ovarian Disorders.—During the past few years there have been several references in the literature to the possibility of stimulating the function of the ovary in cases where this function is depressed by the employment of small doses of Roentgen ray irradiation and on the whole the reports have been of a favorable nature. In the Mayo Clinic, according to FORD (*Radiol.*, 1931, 16, 936), 47 cases were treated with Roentgen ray for habitual amenorrhea or oligomenorrhea or sterility associated with these conditions and 29 cases were treated for dysmenorrhea. The dosage employed was approximately 5 to 10 per cent of an erythema dose. Of the 47 cases treated for amenorrhea, ranging in age from 19 to 37 years, 36 were irradiated over the ovary, 5 over the pituitary and in 6 there was combined treatment of both ovary and pituitary. The report of the results is not available in 6 patients, 15 failed to react, while in the remaining 26 cases menstruation was reestablished within 6 weeks after the treatment and has continued regularly in the majority of patients for periods varying from a few months to 2 years. Seven pregnancies have occurred among 6 of the 24 married patients, all of whom had previously been sterile. Of the 29 cases of severe dysmenorrhea, relief of pain followed the irradiation in 18. Although the duration of relief is extremely variable, by repeated irradiation a satisfactory result has been obtained as long as $3\frac{1}{2}$ years in 1 case. Evidence has not been found that repetition of treatments at intervals of 3 months or longer has adversely influenced ovarian function.

Cancer of the Cervix.—The experiences of the staff of the Memorial Hospital in New York City with irradiation in the treatment of cancer of the cervix are always of interest. In reporting a series of 1574 cases of this disease, HEALY (*J. Am. Med. Assn.*, 1931, 97, 1680) describes the development of his technique up to the present time and the results obtained. As 2 out of 3 of their cases are well advanced when first seen, they give preliminary Roentgen irradiation which shrinks the lesion and gets rid of the softer, friable, infected surface, especially with the use of warm antiseptic douches, thereby creating a more favorable setting for the radium which is applied from 10 to 14 days afterward. Interstitial irradiation is no longer used but the radium is applied by means of various types of applicators in the primary treatment. Interstitial radiation in the form of gold-filtered radon seeds is reserved for use, from 4 to 8 weeks after the primary treatment has

been finished, in any residual part of the original lesion that is not regressing satisfactorily, but the tendency is to use this type of treatment less and less. Similarly the cautery is seldom used to remove large cauliflower masses, since this is usually done with an endothermic wire snare. The application of further radiation to lesions once fully irradiated is considered useless if not dangerous. If the primary lesion is radioresistant he believes that panhysterectomy should be done if the case is favorable for such a procedure. In this series 5-year cures were obtained in 55 per cent of the early cases, 34.6 per cent of the borderline cases and in 15 per cent of the advanced cases. There are very few cases which are cured if the disease develops under 30 years of age. The smaller the lesion and the more localized the disease to the portio vaginalis, the better the prognosis. The more embryonal the cellular structure of the lesion and the greater the degree of anaplasia, the more radiosensitive the lesion will be and the better the prognosis under radiation therapy. Under surgical treatment, on the other hand, this type of lesion gives a bad prognosis, as it is highly malignant and rapidly invades the perivascular lymphatics. Pain is a bad symptom, and when referred to the hips and thighs is usually an indication of incurable disease, located in the retroperitoneal glands and causing pressure on nerves. It is often present in severe form for months before any gross evidence of the metastasis can be detected. Rectal distress due to radiation proctitis is very common in the first month after the treatment and is usually readily controlled by a restricted diet, bismuth and opium by mouth and small olive oil rectal injections. Bladder symptoms are less common but are seen in a small number of cases a year or so after the primary treatment. When seen at this time they are regarded as due to late secondary changes in the bladder mucosa from radiation endarteritis and fibrosis with loss of nutrition to the affected part, resulting in the formation of local trophic ulcers. Such lesions cause severe dysuria and respond very slowly to treatment, which consists of the usual bladder sedatives, irrigations of boric acid solution and instillations of mercurochrome or mild silver protein.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

Choked Disk in Essential Hypertension.—HERMANN (*Deutsch. Ztschr. f. Nervenhe.*, 1931, 121, 281) reports 2 cases of choked disk occurring in patients with essential hypertension. The first patient, a woman, aged 46 years, had had several cerebral accidents, and necropsy revealed general swelling of the brain and extensive hemorrhagic destruction of the right cerebral hemisphere, especially of the parietal lobe, with

evidences of old and recent hemorrhages and areas of softening. The heart was hypertrophied. The kidneys were normal. The systolic blood pressure had varied from 190 to 240 and the diastolic from 105 to 120. The hemoglobin was 110 per cent and the red cell count 5,470,000. The fundi showed bilateral choked disks without retinitis. Central vision was not affected; but left homonymous hemianopsia was present. The second patient, a woman, aged 40 years, complained only of pain behind the eyes. She had bilateral choked disks, right 2 diopters, left 1.5 diopters, with normal central vision and normal visual fields. For 4 years the fundus findings remained practically unchanged except for the development of secondary vessel changes. The systolic blood pressure ranged from 180 to 270 and the diastolic from 120 to 140. The heart was hypertrophied. Neurologically, the patient was negative, both subjectively and objectively. Choked disks are rarely seen in association with apoplectic hemorrhages and softenings, but are not uncommon in traumatic cerebral and in subdural hemorrhages. The appearance of choked disks in the first case can be explained on the basis of the general swelling of the brain and was perhaps influenced by the polycythemia. Lumbar puncture in this case probably initiated the fatal hemorrhage through disturbance of the pressure in the ventricular system. In the second case the choked disks persisted for 4 years without affecting the vision and, since no neurologic symptoms were present, there was no indication for interference. As suggested by Baillart, the edema of the disks in this case was probably secondary to local vascular changes in the optic nerves with resultant active lymph stasis as described by Behr.

Lesions of the Cornea and Conjunctiva in Erythema Exudativum Multiforme.—BAILEY (*Arch. Ophthalmol.*, 1931, 6, 362) states that erythema exudativum multiforme not infrequently shows ocular manifestations of corneal and conjunctival lesions present as an integral part of the general clinical picture of the disease, that its diagnosis is often incorrectly made or confused with other similar diseases, chiefly because of unfamiliarity with its clinical picture. He contends that many of the earlier cases reported in the literature under the caption of herpes iris conjunctivæ are really erythema exudativum multiforme. In 3 cases the clinical features which illustrate the distinguishing characteristics of the disease can be summarized as follows: each began with acute febrile onset and high fever, and developed progressively: (1) generalized, rapidly disseminating, polymorphous skin eruption with macules, papules, purulent bullæ with crusting and petechial rashes; (2) pseudomembranous formation of exudate on the mucous surfaces of the oropharyngeal passages, and in the conjunctival sac associated with marked ocular inflammatory reaction; (3) serious visual impairment due to corneal ulceration and opacification; (4) a clinical course of 2 to 6 weeks. Ocular pathology in these cases and those reviewed in the literature variously included lid edema; marked purulent conjunctivitis with edema, chemosis, subconjunctival hemorrhage, small necrotic hemorrhagic areas and exudate in pseudomembranous formation which quickly reformed and left bleeding points after removal; iris irritation and even anterior or posterior synechia; delayed corneal ulceration, from secondary invasion, which was insidiously progressive and led to

perforation and ectasia or to permanent, dense, deep, vascularized leukoma, to which account for the serious visual impairment. When enucleation is not required, sequelæ are symblepharon, xerosis and stringy, viscid conjunctival discharge, as well as the aforementioned corneal leukoma. The disease is a distinct clinical entity and can be differentiated from pemphigus vulgaris and acute pemphigus by their characteristic skin lesion of blebs in successive crops that rupture and become filled with pus or blood with formation of dirty crusts; from agranulocytic angina by its mild conjunctivitis and characteristic leukopenia; from foot and mouth disease with conjunctival involvement by its uniformly vesicular skin lesion; and from hemorrhagic measles, with which it has occasionally been confused in children, because of the catarrhal type of its conjunctivitis and the uniformity of its skin rash. Therapeutically the author has been lately using large intravenous doses of bacterial vaccines with some promise of success.

Hemorrhage in the Anterior Section of the Eye in a Case With Blue Sclera.—VOGELSANG (*Klin. Monatsbl. f. Augenh.*, 1928, 81, 684) reports a spontaneous hemorrhage into the anterior chamber in a 31-year-old woman with definitely blue scleræ of the hereditary type. The hemorrhage occurred suddenly without preceding trauma. The whole anterior chamber was filled with blood so that the iris was not visible. There was a massive subconjunctival and intrascleral hemorrhage. The hemorrhage cleared up in about 3 weeks, at which time no fundus lesions were demonstrable. There was no history of fractures or deafness and no findings of brittle bones or otosclerosis. Physical and laboratory examinations failed to reveal any cause for the hemorrhage. Some cutaneous phlebectasia were present, but no signs of purpura. The patient's myopia was not of a sufficient degree to account for the hemorrhage. The author regards this case as further evidence for the existence of hypoplasia or dysplasia of the mesenchyme in persons with blue sclera, in this instance affecting the bloodvessels as well. Anomalies of the bloodvessels do occur in these patients as in the case reported by Colden, who found sclerosis of the choroidal vessels in a 29-year-old woman with blue scleræ who also had spontaneous petechial hemorrhages on the legs.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DE WAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Influence of Secretions of the Upper Respiratory Tract on Tissue Resistance.—Aware that extracts from certain organs such as testis greatly enhance invasion of tissue by various bacteria and viruses, HANGER (*Proc. Soc. Exper. Biol. and Med.*, 1931, 29, 285) has investigated a similar effect exerted by secretions from upper respiratory tract. In a well-controlled series, rabbits were inoculated in the flank by a virulent strain of *B. leproseptica* admixed with filtered nasal

washings from persons, normal or with acute colds. In about 40 experiments the areas of infection were larger and more necrotic when the nasal secretions were used, than in the controls. The nasal secretions not only facilitated the spread of fresh experimental infection but when injected into a quiescent lesion often caused an exacerbation. Considerable individual variability was encountered in the action of the nasal washings. As a rule, secretions obtained during an acute cold accelerated the infection more than those taken during a normal period. The author believes this phenomenon to be chemical in nature and probably not dependent upon the filterable agent described by Dochez *et al.* Saliva showed a similar though lesser effect. Tears were inert. Washings from rabbits with acute snuffles were as active as human secretions. "Further work is being done to determine whether nasal secretions may play an enhancing rôle for organisms transmitted from one individual to another in the course of natural infection."

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Advances in Electrosurgery.—In radical operations for cancer of the breast KELLY (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 12, 463) has satisfactorily employed the coagulation and cutting current without a single ligature. The duration, he thinks, is much shorter than the average operation. In massive ulcerating cancer of the breast far more is sometimes obtained than was expected in the way of improvement and prolongation of life. The method is suitable for extensive adherent cancer of the uterus. For kraurosis and for cancer of the vulva and clitoris he regards no method as comparable to circumvallation, followed by sharp exsection of the structures.

Quantitative Roentgen Diagnosis of Pleural Effusions.—Postmortem chest films made by BOWEN (*Radiol.*, 1931, 17, 520) show a wide variation in regard to the demonstration of pleural adhesions. Often rather large effusions failed to cast a characteristic shadow. It was noted also that in cases of bilateral effusion the roentgenologic estimate was not correct as to which side of the chest contained the greater quantity of fluid. The author thinks that the failure to find fairly large effusions (400 to 600 cc.) in many cases either by physical diagnosis or roentgenography is due to the distribution of the fluid which varies in different cases according to the combination of the physical factors present. He believes that small effusions can best be demonstrated in the lateral decubitus.

Roentgenologic Study of Pulmonary Metastatic Growths.—Two hundred and four cases of pulmonary metastasis are reviewed by KIRKLIN and OCHSNER (*Radiol.*, 1931, 17, 435). In order of frequency the primary tumor was chiefly in the breast (90 cases), testis, uterine cervix, bowel or rectum, kidney, thyroid and ovary, with a lower proportion from malignant tumors in other situations. In metastasis from cancer of the breast the lesions were parenchymal in 88 per cent of the cases, and usually bilateral; when unilateral the right side was involved slightly more frequently than the left. Pleural exudate occurred in more than a third of the cases. The incidence of infiltrative lesions was almost as great as that of discrete nodules. Malignant testicular tumors usually produced bilateral metastasis; no pleural lesions were demonstrable. Carcinoma of the prostate gland gave rise to bilateral metastasis, while that from the bladder was either bilateral or unilateral. Pleuritic exudate was present in all cases of metastasis secondary to cystadenoma of the ovary. Carcinoma of the large bowel frequently produced metastasis; carcinoma of the stomach rarely. There was nothing distinctive in the metastasis from tumors of bone. Melano-epithelioma and squamous cell epithelioma seem to be followed by metastasis more often than is generally believed.

Clinical and Experimental Observations Relative to the Etiology of Cancer.—Citing his previous experiments which indicated that cancer may be the direct result of the removal of fat-soluble vitamins from areas of tissue, BURROWS (*Radiol.*, 1931, 17, 775) devotes this paper to the relation of cancer to infections or degenerations elsewhere in the body. From the study of cancers and benign tumors of the breast, the author believes that these lesions are always secondary to uterine lesions. In women the most common benign tumor is a chronic cystic mastitis, and in a large percentage of these cases gonorrhea may have been the immediate agent offending the sex glands. Lesions of the breast associated with uterine lesions are always precancerous. Cancer develops in them only after the organism has suffered from a specific cachexia from other causes. Dead and abscessed teeth have been most frequently associated with these deteriorating states necessary for the development of cancers of the breast. Such disease of the teeth is frequently associated with cancer of the lips or skin and senile keratoses, some of which have disappeared after removal of the teeth. In the discussion Ernst cautioned against considering only one phase of cancer, which is a problem with many sides. Martin regarded the paper as radical; if the teeth are bad they should be treated, but other measures should not be omitted. Homman had also noted the association of oral sepsis with cancer, but patients having cancer are at an age when oral sepsis is common.

Radiotherapy in Chronic Myelogenous Leukemia.—Under present therapeutic measures leukemia has a natural progression to a fatal end, says GILES (*Radiol.*, 1931, 17, 764). In the acute cases death occurs in a few months, whereas chronic cases may last for 10 years. The average duration of life is $2\frac{1}{2}$ years. Spontaneous remission occurs in a very small percentage of cases. Splenectomy does not modify the evolution of the disease and is not superior to irradiation. Irradiation brings the blood

formula to or near normal for a time, but after splenectomy the blood count remains qualitatively leukemic. Although the bone marrow is the seat of the pathologic process, irradiation of the spleen is more effective than treatment applied to the long bones. Nevertheless, the effects are only temporary and recurrences develop; the latter in turn can be repressed by renewed irradiation. Finally the spleen develops a resistance to the treatment and at last therapy becomes entirely ineffective. The frequency of treatment should be determined by the leukocyte count which should not be depressed below 30,000. The smallest effective dose should be employed at the beginning and then gradually increased as resistance develops.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
DENVER, COLORADO.

Investigations Into the Prolonged Treatment of General Paresis with Tryparsamide.—TENNENT (*J. of Ment. Sci.*, 1931, 77, 86) submitted 50 cases of general paralysis to treatment by tryparsamidé. Seventeen were treated by this drug alone, and in 33 others the drug was combined with fever therapy. Of these, 36 per cent have had a good remission, 32 per cent have had a partial remission, 14 per cent are unimproved and 18 per cent are dead. The effect of treatment is influenced by the duration of the mental symptoms prior to treatment, by the age of the patient and by the clinical type of the illness. The chances of successful outcome after treatment diminished into direct ratio to the duration of the mental symptoms prior to treatment. The chances of remission are diminished with the increase of years over 40 years of age. The most favorable types in order of degree of improvement are the manic type, the euphoric type, the simple type and the taboparetic type. The outlook is much better in the simple apathetic type than in the simple fatuous type. The speech defect and the tremors have been the neurologic signs which showed the most improvement as a result of treatment. The changes in the reflexes were slight and inconstant, also in the pupillary reactions. In the early stages the clinical and serologic changes do not run parallel. Complications resulting from treatment by tryparsamide are very few. This drug is considered as highly valuable in the treatment of general paralysis and the results here obtained were considered encouraging.

Cerebral Trauma and Its Relation to Mental Deficiency.—WINKLEMAN (*Am. J. of Psychiat.*, 1931, 10, 611) concludes from his studies that: (1) Cerebral trauma plays a part in the deterioration of adults

and arrested development of infants; (2) subarachnoid bleeding calls for repeated spinal drainage in order to lessen the after results; (3) encephalography gives visual proof of the posttraumatic atrophies present mainly in the fluid field, the frontoparietal area; and (4) dehydration offers a means of improving the mental condition of both the infantile and adult traumatic cases.

The Significance of Cholesterol in Cellular Oxidation and Its Bearing on Mental Disorder.—SHAW and SHARPE (*J. of Ment. Sci.*, 1931, 77, 53) demonstrate the following facts: (1) The inhibitory influence of cholesterol on hemolysis and its activation by lecithin, also the presence of a thermolabile ferment in serum which activates hemolysis, and which appears to vary directly with the blood-cholesterol content. (2) The influence of cholesterol as a controlling factor in oxidative processes, its controlling power being best exercised in relation to lecithin in the ratio to that substance normally existing in the blood. (3) Lecithin has an attractive influence on potassium ions, and the presence of cholesterol in the membrane definitely retards diffusion of potassium. (4) The retarding effect of cholesterol on the anionic movement of colloidal lecithin. (5) Increase of protein diet has no effect in stimulating metabolism in dementia precox. (6) The blood-cholesterol content in dementia precox is greatly diminished, while abnormal increase is noted in states of mania. (7) In general paralysis there is great diminution of cholesterol in the brain substance.

A Qualitative Study of Behavior Problems in Relation to Family Constellation.—LEVY (*Am. J. of Psychiat.*, 1931, 10, 637) finds in a clinical survey of the population of Chicago the distribution of children's behavior problems for the most part to be independent of the size of the family. In a small rich community, families in which there is only one child may produce problem children more frequently than other sized family groups, but this finding is true only of boys; girls do not appear to be often recognized as problems in such districts. In a large city boys come to the attention of the psychiatrist twice as often as girls; and the first born child is a problem child relatively more frequently than children in any other ordinal position. This holds after allowance has been made for the fact that there are more first-born children in the community. The second-born child is a behavior deviate relatively more frequently than children in other ordinal positions only when a small high-grade community is studied. The sex of the siblings nearest in age to the problem child may have a bearing upon the incidence of these problem children. The only child does not appear to be a spoiled child as frequently as children from two-children families—if one accepts personality and emotional difficulties as the outward manifestations of a spoiled child. Only children are troubled more by scholastic difficulties than children with brothers and sisters. The only child commits more acts of delinquency than children with one brother or sister. But most delinquents appear in very large families where economic and social conditions are more important than family inter-relationships.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Work of the Heart Under the Influence of Arteriovenous Aneurysms.—GLEY and GOMES (*J. de Phys. et de Path. Gén.*, 1931, 29, 442) estimated the output of the right ventricle, and recorded the arterial blood pressure, with a large arteriovenous communication both open and closed, in an anesthetized dog. From these findings the work of the left ventricle with the communication both open and closed was calculated. The output of the right ventricle was estimated thus: the expired air was collected in a Tissot spirometer over a measured interval of time. The air was analyzed and the amount of CO_2 given off in 1 minute was calculated. At the same time samples of blood were taken from the right ventricle by means of a cannula introduced through the right jugular vein and from the carotid artery. The CO_2 content of the samples was calculated and the difference between the amounts of CO_2 in 1 cc. of venous and arterial blood was found. The amount of blood passing through the lungs, that is the output of the right heart was calculated from the formula: $E = d \times V$. Where E is the number of cc. of CO_2 expired in 1 minute, d the difference between the amounts of CO_2 in 1 cc. of venous and arterial blood, and V the number of cubic centimeters of blood passing through the lungs in 1 minute. The right heart was found to put out 881 cc. of blood per minute. After uniting the central ends of the left carotid artery and the left jugular vein by a curved cannula the output of the right heart was again estimated and was found to be 2.252 liters per minute. The communication was closed and the output of the right heart fell to 1.005 liters per minute. The mean blood pressure in the carotid artery as measured by a mercury manometer while falling steadily during the experiment was not altered by opening or closing the arteriovenous communication. The work of the left ventricle was calculated from the formula $T = P \times V$, where P is the mean blood pressure in centimeters of water, V the cardiac output in a unit of time and T is the work in kilograms per minute. The work of the left ventricle with the arteriovenous communication closed was found to be 1.72 kg. per minute. With the communication open the work was found to be 3.84 kg. After closing the communication the work fell to 1.76 kg. per minute. The work done by the left ventricle became, therefore, 2.2 times greater under the influence of an arteriovenous communication.

Observations on Variants Derived from Two Strains of Streptococcus Hemolyticus.—GALLAGHER (*J. of Bact.*, 1931, 22, 363) studied 18 strains of Streptococcus hemolyticus with special reference to colony morphology. Of these, 11 were from throat: 7 from scarlet fever, 3 from streptococcic sore throat, 1 from acute follicular tonsillitis; 5 were from blood cultures; 1 was from pleural fluid; 1 was from an area of diabetic gangrene. The organisms were isolated on blood agar, then seeded on chocolate agar. After incubation for 24 hours, the colonies

were studied grossly and under low power of the microscope with reflected light. Of the 18 strains of *Streptococcus hemolyticus* carried on infusion agar without blood for from 17 to 170 transplantations only 2 strains showed permanent changes in colony morphology and exhibited ability to give rise to glossy variants. These grew with difficulty in the presence of whole unheated blood, were unable to produce so potent a toxin as their matt forms as tested by Dick and Dick's method, and were able to change the color of chocolate agar to a light greenish-brown shade. One of these variants after 7 generations in 1 per cent *N* rabbit serum broth gave rise to a rough or pebbly form which was serologically identical with the glossy form and preserved its ability to change the color of the chocolate agar. Repeated cultures from patients with scarlet fever and erysipelas were all of the matt type of colony.

Variations in the Manifestations of Rheumatic Fever in Relation to Climate.—A study of the geographic distribution of rheumatic fever and the relationship of climate to symptomatology was undertaken by LONGCOPE (*Ann. Int. Med.*, 1931, 5, 401) and a review of all cases of rheumatic fever coming under observation at the Johns Hopkins Hospital over a 5-year period was made. Out of a total of 10,386 adult admissions, 142 or 1.37 per cent suffered from rheumatic fever in an active, quiescent or possibly healed stage, the total mortalities being 16.2 per cent. Over 95 per cent of this series showed cardiac disease on admission or developed signs of cardiac involvement during the period in hospital. In over 50 per cent of the series a history of either cardiac disease alone or in combination with some other rheumatic manifestation was obtained. In only 26 per cent was there a history of arthritis without a history of some cardiac disease, while in 19 per cent there was no history of any rheumatic manifestation except tonsillitis. Males and females were attacked in equal proportions, rheumatic fever being more common in the white than in the colored races. The incidence of auricular fibrillation increases with age, while cases of bacterial endocarditis are more frequent in the young. Out of 135 cases, mitral stenosis and insufficiency were present in 76, while mitral stenosis and aortic insufficiency were found in 50. In 9 of the 22 autopsies in this series death was associated with some form of acute rheumatic carditis. Many agree, from the study of a large amount of clinical material, that rheumatic fever is extremely rare among the natives in tropical climates whereas in the colder portions of the temperate zone the condition is extremely common, being less frequent in the warmer portions of the temperate zones. According to Coburn, its distribution corresponds to scarlet fever. In the tables published the lowest incidence is found in Atlanta, Georgia, only 2 cases occurring in 2500 hospital admissions (0.08 per cent) while the highest incidence is in Johannesburg, South Africa, where 159 cases were seen in 2906 admissions (5.8 per cent). In some regions, as in China where rheumatic fever is said to be rare, mitral stenosis is often found. The author observed that it was probable that the disease might be detected more frequently in semitropical countries if it were regarded as primarily a disease of the heart. In Baltimore, while the severe forms of arthritis are uncommon, cardiac disease, often of insidious origin, is very frequent, its incidence being somewhat higher than in other series of rheumatic fever in the literature.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Influence of Artificial Fever on the Course of Experimental Poliomyelitis.—JUNGEBLUT and KOPELOFF (*J. Infect. Dis.*, 1931, 49, 348) state that within the limitations of the experimental material, it appears to be proved that noninfectious fever of considerable intensity applied during the period of incubation, but maintained only over comparatively short periods of time, is not capable of altering the course of experimental poliomyelitis in the monkey to any significant extent. The same holds true for infectious fever produced by inoculation with *Trypanosoma equiperdum*, where the two infections are induced simultaneously. With a poliomyelitis infection superimposed on an existing febrile trypanosomiasis there may be a distinct prolongation of the period of incubation of the poliomyelitis infection, undoubtedly indicating some attenuation of the virus. Since the latter observation is based on one monkey alone, it is not known how regular this occurrence is. With syphilis a definite spirocheticidal effect *in vivo* may apparently be obtained by febrile temperatures that cause no obvious damage to the host. As regards poliomyelitis, it would seem that the production of a sufficiently intense fever to bring about destruction of the virus *in vivo* is not possible within a safe zone of raised temperature.

The Influence of Heredity Upon the Incidence of Lung Tumors in Mice.—LYNCH (*J. Exper. Med.*, 1931, 54, 747) crossed a male mouse from a strain with a high incidence of spontaneous lung tumors with several females derived from a low tumor strain. The first generation of offspring were then backcrossed to individuals of the original strains. The resulting two groups of offspring differed significantly in the incidence of spontaneous tumors of the lung. These facts are discussed in relation to others previously discovered. It seems clear from the evidence presented that there are among mice constitutional types which differ in incidence of tumors of the lung and that the differences are inherited. The number of genetic factors involved has not been determined. No influence of sex was apparent. The possibility of there being genetic factors which affect tumor age will be dealt with later.

A Water-borne Typhoid Fever Outbreak With Unusual Epidemiologic Features.—SEARS (*Am. J. Pub. Health*, 1931, 31, 1019) declares that as the spoor of the wild animal unerringly leads the hunter to his prey so it is that certain epidemiologic data just preceding the outbreak of typhoid fever blaze the trail to be followed in speedily tracing its source. The average age of the victims (in this instance 29.4 years) gives us a strong hint as to whether it is a milk-borne or water-borne

outbreak, but what is of greater value in tracing water-borne outbreaks is the knowledge that dysentery and diarrhea have immediately preceded the typhoid cases in the same locality, and it was this fact that placed the investigators on the water-borne trail in the epidemic described in spite of the fact that only a small area of the village was infected, and the only food or drink which was partaken by all of the victims was the water from the common village supply. By following this trail the source was located within a few hours and further infection checked. The excellent service rendered by the Red Cross undoubtedly prevented a much higher death rate. No well organized hospital could have given more adequate and efficient care than was given by the Red Cross service in this temporary hospital. Cross-connections between a city water supply and a water supply of doubtful purity for manufacturing plants or other purposes should never be tolerated. No mechanical device for protection is fool-proof, and all devices designed to protect municipal water supplies against water of questionable purity have been legally eliminated in New York State since July 1, 1926.

Etiology of Influenza: Experiments in Chimpanzees With Filtered Material Derived from Human Influenza.—LONG, BLISS and CARPENTER (*J. Am. Med. Assn.*, 1931, 97, 1122) transmitted disorders characterized by fever, prostration and a leukopenia to three chimpanzees by intranasal inoculation with bacteria-free filtrates of rhinopharyngeal washings obtained from individuals ill with human influenza. A similar condition has been produced in an ape during a nonepidemic period by means of intranasal inoculation with unfiltered influenzal material which had been preserved in the icebox for 123 days. The difficulty of interpreting with complete satisfaction the observations made on the apes is obvious, and therefore the observed facts are presented with the knowledge that they conform with those previously reported in man by other investigators.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 16, 1932

Variability of Pigmentation in the Hypophysis and Parathyroids of the Gray Rat (*Mus Norvegicus*).—W. H. F. ADDISON and DORIS A. FRASER (from the Department of Anatomy, University of Pennsylvania). Melanotic pigment is present in the hypophysis of the adult Norway rat, both wild and captive, in the majority of cases. When present it is usually confined to one part of the organ and visible on direct inspection. It is seen most frequently in the pars intermedia, but is also found in the pars distalis and on the margins of the pars nervosa. The pigment is in melanophores, which have a number of characteristic branching processes. These lie in the connective-tissue septa.

There is no apparent difference in the incidence of pigmentation in males and females, nor is there any observed relation of gestation to

pigmentation. Pigmentation within the pars intermedia was seen as early as at 2 months of age, but is not of constant occurrence even in old rats.

Pigment within the parathyroids has been found in a small number of cases, in both wild and captive gray rats. The pigment cells lie in the connective-tissue septa between the epithelial cell masses, but has not been seen in the adjoining thyroid. When present, it may occur in only one of the parathyroids, or in both. The parathyroids may be pigmented in the presence or absence of pigment in the hypophysis.

The material for the study of the wild gray rats came from the Philadelphia Zoological Gardens. The captive grays belonged to Dr. Helen D. King's strain of captive gray rats, which was begun in 1919 at The Wistar Institute of Anatomy.

The Magnitude of the Retinal Potential of *Limulus* as a Function of the Number of End-organs Illuminated.—C. H. GRAHAM (from the Eldridge R. Johnson Foundation for Medical Physics, University of Pennsylvania). The effect of varying the area illuminated is one of the most important problems confronting workers in the physiology of vision, because results obtained in past analyses have shown that this approach is one which offers the best route to the question of end-organ and synaptic function in the visual response. The investigations of Adrian and Matthews in particular have stressed the importance of the latter activity. On the basis of their experiments nobody can deny the contributions of the synapses. On the other hand we are still left with the question as to how to separate the influence of the end-organ with its attached neurone from the influence of the synaptic connections. Stated in slightly different language the question which arises is this: What is the contribution of the single end-organ *per se* undistorted by activity at the synapse?

The eye of *Limulus polyphemus* is well suited for this determination. In the eye of this animal there are neither synapses nor ganglion cells, and it would seem for this reason that here, if in any animal, we should be able to analyze the visual process in its simplest terms. The problem which has been studied concerns the question of how the magnitude of the retinal potential varies with the number of end-organs illuminated.

Measurement of the retinal potential in the excised eye has been made by means of a resistance-capacity coupled amplifier and a ballistic galvanometer. This technique is legitimate in the case of *Limulus* because the retinal potential is a simple wave.

Extent of the illuminated area has been controlled through the use of diaphragms placed directly against the eye. Anatomic checks as to the number of ommatidia illuminated have been performed by clearing away the tissue and pigment from the back of the eye after each experiment and taking photomicrographs of the back of the illuminated region—a photograph for each size of diaphragm used. In this manner it is possible to count directly the number of ommatidia illuminated.

Results obtained under these conditions show that the magnitude of the retinal response is a linear function of number of ommatidia illuminated. A plot of retinal response against number of ommatidia for various intensities gives a family of straight lines whose slopes are determined by the logarithm of the intensity. The linear relation holds up to the limits of one-half to two-thirds of the total number of oma-

tidia in the eye. Beyond this point the curve flattens and finally the response is independent of number. The "tailing off" may be interpreted as being due to the angular displacement of the peripherally located ommatidia.

These results would seem to indicate that the retinal excitation process in *Limulus* is simple. They give justification for assuming that each end-organ contributes its share to the state of excitation, and that this state, insofar as end-organ contribution goes, is determined by the number illuminated.

Study of the Relationship of Arterial, Cutaneous and Venous Blood Sugar.—LEON JONAS (from the George S. Cox Research Institute and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania). The basis of this report is a study of the relationship between the concentration of glucose in cutaneous, arterial and venous blood in normal individuals and in certain pathological conditions.

The sugar concentration in the cutaneous and the arterial blood was studied in 3 males without obvious circulatory or metabolic disturbance 1 hour after 1 cc. of epinephrin and in 4 male subjects 1 hour after 100 gm. of glucose. The sugar values agreed within the limits of error of the method in 5 of the 7 determinations; the remaining 2 cases were within 8 per cent.

The cutaneous and venous blood, taken after fasting, contained the same concentration of glucose, or nearly so. However, when the blood samples were taken from $\frac{1}{2}$ to $1\frac{1}{2}$ hours after 100 gm. of glucose the cutaneous blood always contained a higher concentration of glucose than did venous blood.

We found that heat and cold had no influence on the cutaneous venous difference. In 4 experiments on 4 subjects the left arm was placed in a water bath at a temperature of 45° F. and the right in a bath at 20° F. for 1 hour after taking 100 gm. of glucose. At the end of that time blood was withdrawn from a vein at the elbow and then from the finger as simultaneously as possible and then repeated on the other arm. The blood was collected without the use of a tourniquet.

In 3 experiments on 3 subjects the cutaneous venous differences were the same for both arms. In the one individual in whom there was a difference the same difference was found on repeating the experiment with both arms at room temperature.

In 9 normal males and 9 normal females it was found that there is a tendency to greater cutaneous venous blood sugar difference at the crest of a sugar-tolerance curve in the female than in the male. In a study of thyroid disease this difference is exaggerated in hypothyroidism, diminished in hyperthyroidism. Inferences from these facts as to rates of sugar utilization in the peripheral tissues ought, however, to be drawn with caution unless data are at hand relative to rate of blood flow through the part drained into the vein, a factor which will also influence these cutaneous venous differences.

Comparative Studies of Glucose and Phosphate Concentrations in Blood Plasma, Glomerular Fluid, Aqueous Humor, Cerebrospinal Fluid and Lymph.—A. M. WALKER, E. H. ELLINWOOD, and J. A. REISINGER (from the Laboratory of Pharmacology, University of Pennsylvania).

Macrocolorimetric methods for the determination of reducing substances (Sumner) and inorganic phosphates (Küttner) have been adapted to use in small glass capillary tubes so that quantitative analyses may be done upon 0.2 c.mm. of fluid or plasma. In control experiments on aqueous solutions the error of duplicate determinations was rarely more than 5 per cent. The results of microdeterminations upon plasma agreed well with those of macrodeterminations by the Hagedorn-Jensen and Küttner methods, and quantitative recovery has been made of sugar and phosphate added to dialyzed plasma.

All of the plasma glucose and phosphate of frog, necturus, horse and man was found to be filtrable through artificial membranes of cellophane or paralodion. In 61 experiments the sugar or phosphate concentration of glomerular urine obtained from the frog and necturus was compared with the concentration of these substances in the plasma. The mean glomerular urine contained 97 per cent as much sugar, 100 per cent as much phosphate as the plasma. In 12 experiments the sugar and phosphate concentration of lymph obtained from the frog's web was found to be nearly identical with the concentration of these substances in plasma. The similarity thus demonstrated between glomerular fluid, lymph and plasma in respect to sugar and phosphate is believed to reinforce previous evidence obtained in this laboratory which indicated glomerular fluid to be a filtrate of plasma.

Cerebrospinal fluid obtained from the frog was found to contain only 66 per cent as much sugar and 39 per cent as much phosphate as plasma. Aqueous humor obtained from the frog was found to contain only 63 per cent as much sugar and 42 per cent as much phosphate as plasma. Since these results upon aqueous humor are in conflict with results previously reported upon mammals, similar comparisons were performed upon a series of 13 mammals and 2 humans with confirmatory findings. The difficulty of reconciling these results with the prevalent conceptions of cerebrospinal fluid and aqueous humor formation was pointed out.

Observations on the Action of Bichloride of Mercury on the Frog's Kidney.—K. A. ELSOM and A. N. RICHARDS (from the Laboratory of Pharmacology, University of Pennsylvania). Experiments have been made concerning the action of bichloride of mercury on the kidney. The kidney of the frog was selected since its structural details can be observed microscopically during life. Bichlorid of mercury (0.3 to 0.5 mg.) was injected subcutaneously. Within 48 to 72 hours the urine elimination had diminished or ceased. The animals became edematous, and there was decrease in the plasma protein content. Microscopic examination of the kidney of such a frog revealed an unusually active glomerular circulation. Normal or excessive quantities of glomerular fluid could be collected, although no urine issued from the ureter.

Experiments on the excised kidney, and the living kidney *in situ*, demonstrated that the tubules of the poisoned kidney were unable to retain phenol red, or to concentrate the dye by the selective reabsorption of water. The urinary elimination of phenol red was very imperfect; in consequence there was retention of the substance in the body.

Urea, ordinarily concentrated many times in its passage through the normal tubule, was only slightly concentrated by the poisoned

tubule. The inadequacy of the bichlorid kidney in eliminating urea resulted in its accumulation in the blood.

Glucose and chlorid, substances reabsorbed from the normal tubule, failed to be reabsorbed in normal amount from the poisoned tubule, and were found in abundant quantities in the urine. In all respects studied the urine from bichlorid frogs resembled a relatively unelaborated glomerular filtrate.

Experiments were made in which the glomerular vessels of the normal frog's kidney were perfused with Clark's modification of Ringer's solution, and the renal portal vessels were perfused alternately with Clark's solution and horse serum. The urine elimination was markedly reduced when horse serum was flowing through the renal portal vessels. Similar results were obtained when hypertonic solutions (1.5 times physiologic) of sodium chlorid or glucose were perfused through the renal portal vessels. The conditions of the experiments were such that increased tubular reabsorption, induced passively by the increased osmotic pressure of the fluid which bathes the tubules, is the only adequate explanation for the reduction in urinary elimination. An experiment was cited in which this reduction in urine output, caused by hypertonic saline solution, was greatly exaggerated after tubular vitality had been destroyed with potassium cyanid. These perfusion experiments confirm and strengthen the belief that the anuria in bichlorid kidneys is due, in part at least, to the fact that the osmotic pressure of the blood proteins, unopposed by the normal tubular epithelium, draws all or nearly all of the glomerular filtrate back into the blood.

Red Blood Cell Counts and Hemoglobin Determinations in a Single Specimen of Blood by Means of a Photoelectric Cell.—J. H. CLARK, T. V. LETONOFF and C. S. ROBB (from the Laboratories of the Philadelphia General Hospital). In an endeavor to simplify the method of counting red blood cells and determining hemoglobin for clinical use, and to eliminate the tediousness of the process and personal element as far as possible, use was made of a photoelectric cell, a single specimen of blood and the well-known benzidin reaction for occult blood.

The extremes of current flowing through a Westinghouse photoelectric cell, that is from zero light to maximum light, were made to correspond to the 0 and 300 reading on a Weston horizontal microammeter, by means of one stage of amplification in a modified standard circuit. The light source could be varied from a 6-volt 32-candle-power automobile headlight to a 110-volt 400-watt projection bulb and the same relative scale readings maintained by varying the amplified current through the meter. The current due to the light on the photoelectric cell is first standardized against tap water for the 0 to 300 microammeter reading. Its stability is checked against a stable solution of potassium ferrocyanid and ferric ammonium sulphate as a standard. With the latter solution practically constant microammeter readings should be obtained from day to day.

Blood was collected in a Trenner automatic pipette, and an isotonic diluting fluid of sodium oxalate and sodium chlorid used. By means of the photoelectric cell, the number of red blood corpuscles in suspension was obtained from the microammeter reading on a graph, standardized against actual blood counts from finger tip and oxalated blood.

The possible effect produced by difference in size of the red blood cells, as shown by the volume index, was also considered. Further data are being collected on this phase, but our present figures would indicate an accuracy well within 150,000 cells per c.mm.—the accepted limits for routine counts.

The hemoglobin was determined by a modification of the benzidin reaction. The optimum conditions of the reaction have been found to depend very specifically on the concentration of the benzidin, acetic acid and hydrogen peroxid. With the concentrations used we have been able to obtain, with small quantities of blood, a constant clear blue color of a suitable density to be used with the photoelectric cell. In order to obtain accurate and reliable results the method must be very accurately controlled, the reagents made in a quantitative manner and used exactly as given below.

With the standardized and tested photoelectric cell it was found that the maximum development of the benzidine blue color occurred in from 4 to 6 minutes. Variations of temperature from 19° to 30° C. had no effect on the speed of development or intensity of the color. The amounts of reagents in their order used at the present time are as follows: Blood, 0.1 cc., 1 to 200 dilution in an isotonic sodium oxalate-sodium chlorid solution; benzidin (purified), 4.5 cc. 0.02 per cent aqueous solution; acetic acid, 0.2 cc. $\frac{N}{10}$ solution; hydrogen peroxid, 0.2 cc. 3 per cent solution. The color is developed at room temperature for 5 minutes and the grams of hemoglobin per 100 cc. obtained from the microammeter reading on a graph, standardized against oxygen combining capacities.

Hemoglobin was determined with an accuracy unexpected in minute amounts of fluid corresponding to 0.0005 cc. of undiluted blood, equivalent to as little as 0.01 to 0.02 mg. of hemoglobin. The method as outlined is accurate to within 1.6 per cent error, with an equal number of determinations above and below the amount found by the van Slyke oxygen combining capacity method.

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ORIGINAL ARTICLES.

BRAIN TUMORS.

A REPORT OF THE TYPES SEEN IN GENERAL PRACTICE.

BY ROBERT ZOLLINGER, M.D.,

AND

ELLIOTT C. CUTLER, M.D.,

CLEVELAND, OHIO.

(From the Department of Surgery of the Lakeside Hospital, Cleveland, Ohio.)

THE syndrome of headache, vomiting and failing vision is indicative of increased intracranial pressure. When the history is of a progressive nature this syndrome suggests the general diagnosis of tumor of the brain. The direct measurement of intracranial pressure by lumbar puncture is somewhat difficult and, in the presence of a posterior fossa tumor with considerable pressure, may be dangerous to the welfare of the patient. Two of the most valuable procedures for detecting increased intracranial pressure are the examination of the eyegrounds and the determination of changes in the skull by means of the Roentgen ray. Evidence in roentgenograms of increased intracranial pressure is based chiefly on the number and depth of convolutional impressions, atrophy of bone about the sella and the base of the skull and separation of the sutures in children. Papilledema usually occurs early in cases of increased pressure and is sufficient evidence of the increased tension without additional confirmation by lumbar puncture. However, large noninvasive tumors which arise from the arachnoid may be present without signs of increased intracranial pressure. These tumors often grow so slowly that the flow of cerebrospinal fluid

remains unobstructed; localized intracerebral edema is uncommon and signs of pressure do not appear until the tumor has reached a large size. This type of tumor, however, often gives local evidence of its presence in the roentgenogram, as shown by an increase in the vascular channels near the lesion, calcification within the tumor or the local bone changes.¹ The slowly growing invasive tumors show the highest percentage of Roentgen signs of increased pressure, usually associated with choked disks.² This is also true in some cases of long-standing posterior fossa tumors which give rise to intermittent blocking of the cerebrospinal fluid pathways. The rapidly growing infiltrating tumors show a marked degree of choking of the disks but may progress so rapidly that Roentgen ray signs of increased intracranial pressure do not have time to develop.

It is important that the family doctor recognize early the complaints resulting from increased intracranial pressure or those referable to local pressure about the sella. Both young and old patients complaining of prolonged headache, or headache and failing vision, should be examined with the ophthalmoscope, the Roentgen ray and, when possible, should have studies of the fields of vision.

A thorough neurologic history and examination, including repeated perimetric tests of the fields of vision and ophthalmoscopic examinations, will usually reveal the position of the growth. The history of the onset and progression of symptoms is of great value in localization. In many cases the neurologic picture is confused by complex symptoms resulting from the marked increase in intracranial pressure. In such a patient, reduction of the pressure by the use of hypertonic solutions may be necessary in order to determine the symptoms directly referable to the tumor. In pituitary tumors constitutional manifestations may call attention to involvement in the region of the sella before signs of local pressure develop.

The Roentgen ray may be of value as an aid to localization if there is calcification within the tumor. Many meningiomata and certain gliomata tend to calcify; this calcification aids localization. It is to be remembered that intracranial calcification may be physiologic rather than evidence of tumor. Areas of physiologic calcification may be found in the choroid plexus, falx cerebri, pachionian bodies and the pineal gland. Calcification within the pineal gland is present in over 50 per cent of the roentgenograms of normal skulls. It may be present as early as the tenth year. In some cases the displacement of the pineal shadow aids in localization of the tumor.

Pathologic intracranial calcification has been classed as either neoplastic or non-neoplastic.³ Hematomata (Fig. 1), old abscesses, tubercles, aneurysms (Fig. 2) and areas of old meningeal disease fall into the latter class. In the neoplastic group are meningiomata, about 70 per cent of Rathke's pouch tumors (Fig. 3), certain slow-growing gliomata, hemangiomas, dermoids and cholesteatomata.

Besides the changes from general increased intracranial pressure or those from focal changes in the tumor the Roentgen ray may be of value in establishing the character, localization and extent of cerebral lesions following the replacement of cerebrospinal fluid by air. This method is frequently necessary when localization by the usual methods of examination is not definite. The replacement of the spinal fluid by air may be done by encephalography or ventriculography. Encephalography is the method of replacement of cerebrospinal fluid with air by means of lumbar or cistern puncture, in contrast to ventriculography which requires trephining the skull and introducing air by way of a cannula inserted through the opening in the skull and through the occipital lobe of the brain into the posterior horn of the lateral ventricle.

Encephalography should not be attempted in the presence of marked choking of the disks or other evidence of well-defined increased intracranial pressure. Frazier says it should not be attempted if the spinal fluid pressure is 20 mm. Hg or above, with the patient over in the horizontal lateral position.⁴ In such cases the intracranial pressure should first be decreased by dehydration. This is accomplished by limitation of the total fluid intake and the addition of hypertonic solution intravenously, or by mouth or rectum. The chief indications, however, may be found in cases with obscure symptoms following trauma or inflammation, in cases of senility, in certain tumors of the brain and in cases where there are cerebral manifestations of uncertain origin. Ventriculography is used when visualization of the ventricles is desired in the presence of increased intracranial pressure, or in cases where encephalography has not been satisfactory. The procedure can be carried out under local anesthesia and is relatively safe, especially if cannulae are placed into both ventricles so that air enters one side as the ventricular fluid is siphoned out of the other. The air should be removed after the roentgenologic studies are completed. A great deal of important information is often gained concerning the cerebrospinal fluid pathways. Although the patients complain of more or less severe headaches, fatal accidents are rare.

For purposes of diagnosis and treatment, tumors of the brain may be divided into four large groups: meningiomata, gliomata, pituitary tumors and perineurial fibroblastomata.

1. MENINGIOMATA. Meningiomata, also known as dural endotheliomata, psammomata, meningeal or arachnoid fibroblastomata, make up about 12 per cent of tumors of the brain. They are usually slow-growing connective tissue tumors which are said to arise from the arachnoid. Recently Bailey and Bucy have described nine different histologic types of meningeal tumors.⁵ They occur chiefly in the anterior fossa, especially in the region of the falx. Although they may press deeply into the brain (Fig. 4), they never infiltrate it; however, they may grow into the overlying

skull, producing exostoses. (Fig. 5, *A* and *B*.) The bony changes which are considered characteristic of these tumors are: (1) Local erosion and vascularity; (2) osteoma formation; (3) spicule formation; (4) diffuse thickening; (5) enlargement of the meningeal channels.

Calcification within the tumor itself is another common characteristic. (Fig. 6.)

A suprasellar meningioma may cause distortion of the sella, and a mistaken diagnosis of pituitary adenoma is sometimes made. It has been found in a large series that the roentgenogram reveals the presence of a meningioma in about 50 per cent of the cases.¹ In a patient with a slowly progressing history suggestive of a tumor of the brain, with or without signs of increased intracranial pressure, the presence of a meningioma is suspected. This type of tumor usually occurs in middle life. However, in the Lakeside Hospital, a large meningioma was found in a boy, aged 10 years. (Fig. 4.) Meningiomata also form a high percentage of the tumors of the brain found in psychotic patients because of the number of these tumors which affect the frontal lobes.⁶

In accessible locations the chance for surgical removal of a meningioma is very good. These tumors are very vascular, and this many times makes the operative procedure difficult. However, since the introduction of surgical endothermy into neurosurgery by Dr. Harvey Cushing, hemorrhage is more easily controlled. Deep-seated tumors may also be slowly scooped out by the electric cutting wire loop. The suspected point of origin of these tumors from the arachnoid may be cauterized, lessening the chances of recurrence. Roentgen ray therapy does not seem to hinder the growth of these tumors.

2. GLIOMATA. About 50 per cent of all tumors of the brain fall into the glioma group. These are the malignant infiltrating tumors which in many cases cannot be completely removed by surgical means. The diagnosis of glioma is not sufficient, however, to give insight into the probable future clinical course. Bailey and Cushing classified gliomata into over a dozen groups, and they were able to show some prognostic significance from a histologic study.⁷ These groups represent certain embryologic stages in the development of the cellular types involved in the histogenesis of the brain. (Fig. 7.)

The types and relation of the tumors of the glioma group are shown in the classification starting from the neuroectoderm and developing into both adult nerve cell and into the adult glial or supporting cell.⁸ Tumors arising from the germinal cells, known as medulloepitheliomata, are found as such in the roof and floor plate of the adult brain, also in the pars ciliaris retinae. These tumors are rapidly fatal.

The majority of gliomata fall, however, into one of three groups. Of the verified gliomata in the Lakeside Hospital, about 43 per

cent are classed as astrocytomata, nearly 30 per cent as spongioblastomata and 20 per cent as medulloblastomata. The remainder are several oligodendrogliomata (Fig. 8), 1 ependymoblastoma and 1 medulloepithelioma. A certain number of gliomata vary markedly in histologic appearance in different parts of the tumor. An effort should be made with simple stains to determine the predomi-

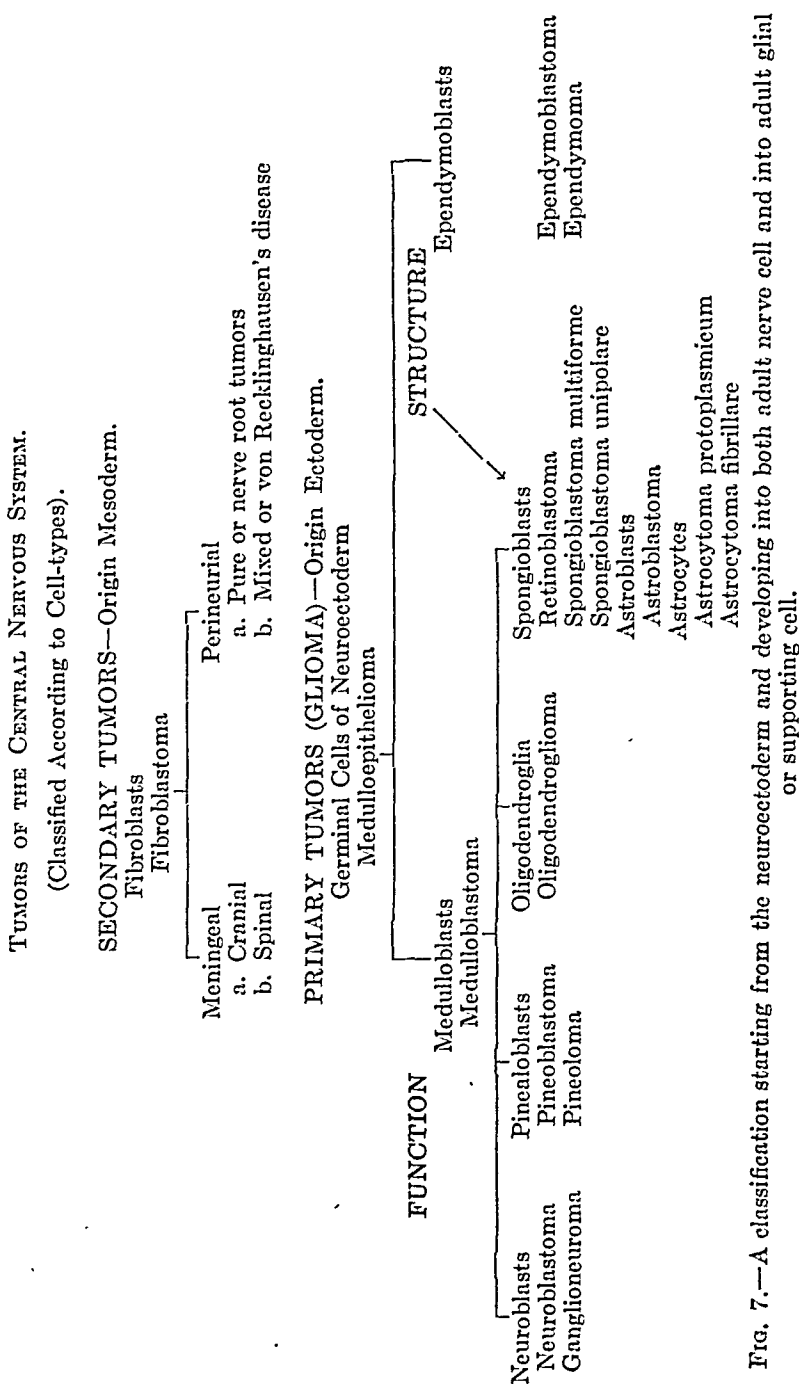


Fig. 7.—A classification starting from the neuroectoderm and developing into both adult nerve cell and into adult glial

nant cell type and group it accordingly, if any prognostic significance is to be drawn from a histologic examination. The histologic picture often changes in a tumor as a result of Roentgen ray therapy or repeated surgical interference.

(a) *Medulloblastomata*. A medulloblastoma is a rapidly growing cellular tumor which usually occurs in the central part of the cerebellum of children. This type of tumor has been referred to as a childhood disease. Valuable time is often lost by treating chronic nausea and vomiting in children as a gastrointestinal upset before ruling out the possibility of a tumor of the brain. These tumors are composed of undifferentiated bipotential or polypotential cells which may differentiate into the various structural or nervous elements of the brain. (Fig. 9.)

Penfield⁹ believes it would be better to consider that these tumors are made up of apolar (migratory) spongioblasts instead of indifferent cells, as he was unable to find neuroblasts in these tumors. With surgery the survival period of these patients is about 15 months. These primitive tumor cells, however, respond well to Roentgen ray therapy which often increases the survival period to 30 months. Roentgen ray therapy does not destroy the growth completely or prevent its growth indefinitely. Surgery should be followed by intensive Roentgen ray therapy. In cerebellar cases this consists of an erythema dose divided into four parts, given at intervals of 2 to 3 days, to alternate sides of the cerebellum. After 1 month to 6 weeks another divided erythema dose is given directly to the base of the skull with the head anteflexed.

(b) *Spongioblastomata*. Spongioblastomata may be divided into two groups: spongioblastoma multiforme and spongioblastoma unipolare. A spongioblastoma multiforme is characterized by multiplicity of cell forms and degenerative processes. (Fig. 10.) It is a rapidly growing cellular tumor composed of immature glial cells, chiefly bipolar spongioblasts. The usual location is in the cerebral hemispheres of adults. Cysts in these tumors are common as a result of degenerative changes and hemorrhage from poorly formed bloodvessels. Hemorrhage into the tumor probably accounts for the sudden severe neurologic symptoms which these patients often develop. This type of tumor with meningiomata forms a very high percentage of tumors in psychotic patients.⁶ These tumors often run their course within a year. A spongioblastoma multiforme, as a rule, responds to Roentgen ray therapy, but not so well as a medulloblastoma. Intensive Roentgen ray therapy should always be combined with surgery.

A few tumors of the spongioblastoma group are composed chiefly of unipolar spongioblasts. (Fig. 11.) This group, known as spongioblastoma unipolare, is composed of very slow-growing tumors, often showing a tendency to calcify. They are said to respond poorly to Roentgen ray therapy. A divided erythema



FIG. 1.—The arrows point to calcification within the brain which at exploration proved to be the result of a vascular lesion (hematoma).

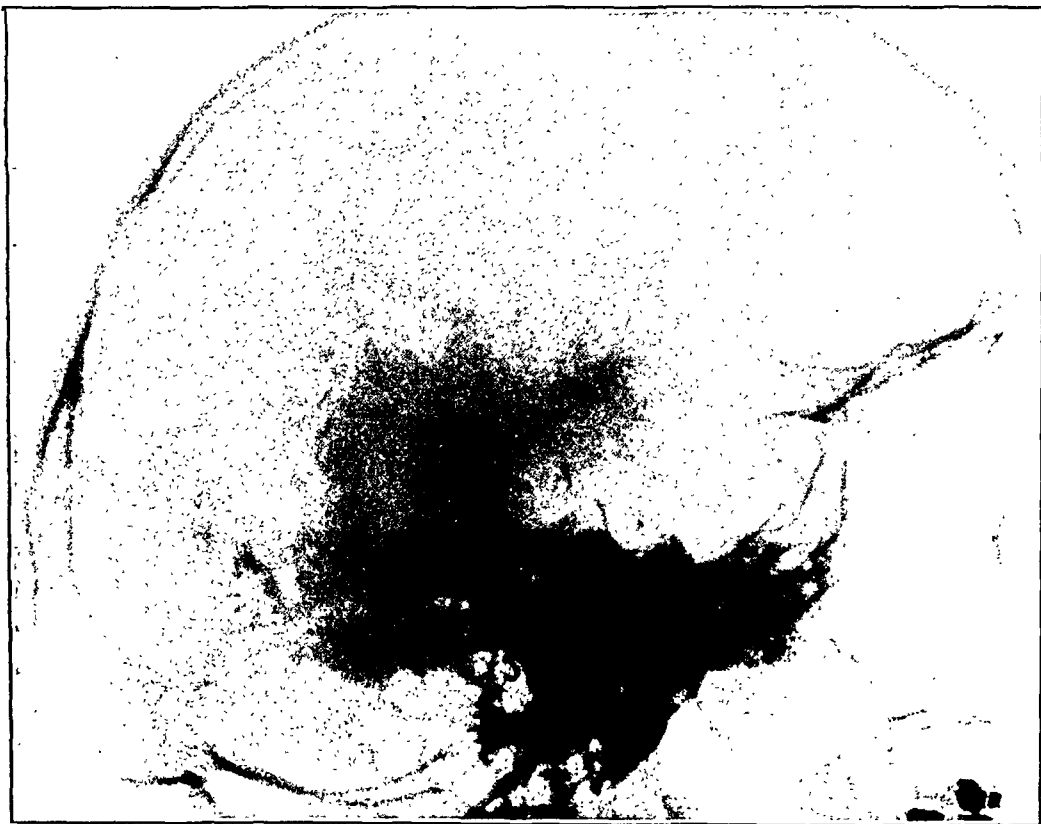


FIG. 2.—Enlargement of the sella and destruction of the posterior clinoids caused by a large aneurysm of the right internal carotid artery. Note the dense linear calcification above the clivus.

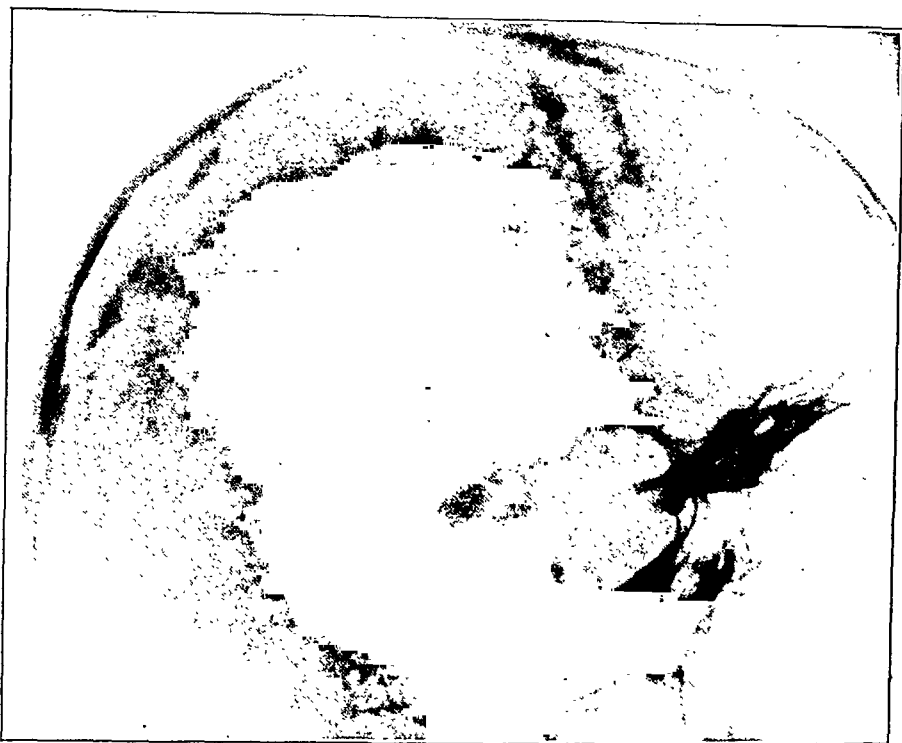


FIG. 3.—Distortion of the sella turcica and suprasellar calcification produced by a Rathke's pouch tumor. Gross tumor shown in Fig. 13.



FIG. 4.—Gross specimen of a large meningioma occurring in a boy 10 years of age. The tumor was easily separated from the surrounding brain substance.



B

FIG. 5.—A. Note the prominence of vascular channels (*a*) in the region of the tumor. Meningioma infiltrating through the skull producing a large exostosis (*b*). B. Anterior-posterior view of Fig. 5, A, showing the fuzzy appearance characteristic of meningiomata infiltrating the skull.

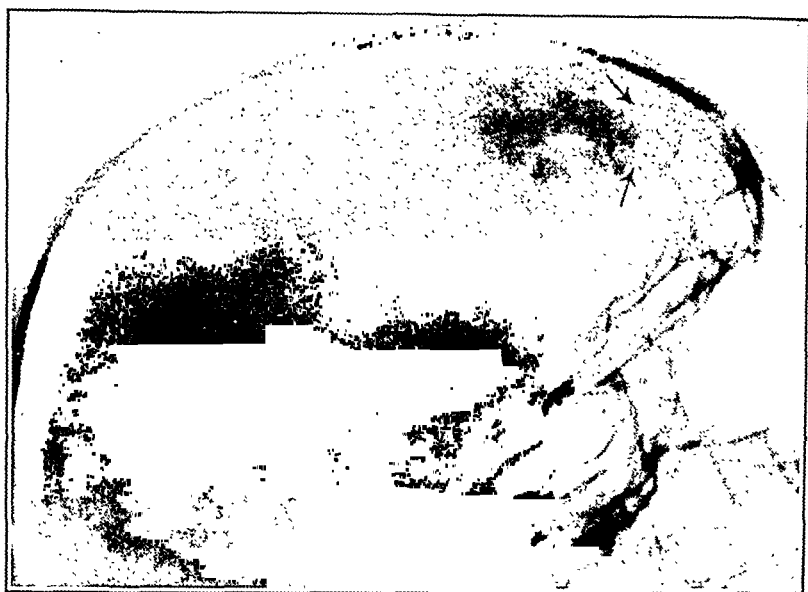


FIG. 6.—The arrows point to an area of calcification within a meningioma.

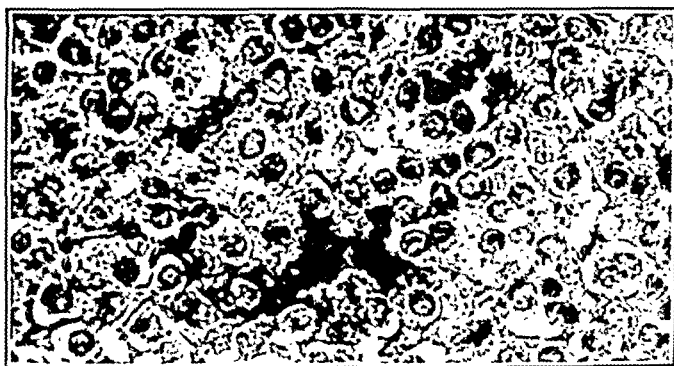


FIG. 8.—Section of an oligodendroglioma showing the spherical nuclei with a heavy chromatin network surrounded by a ring of cytoplasm which stains very feebly.

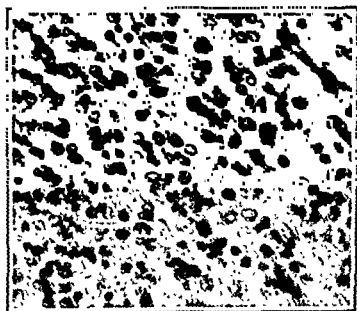


FIG. 9.—Medulloblasts infiltrating around the dark-staining granular cells of the cerebellum.



FIG. 10.—An area of degeneration in a spongioblastoma multiforme giving a "palisade" arrangement.



FIG. 11.—A spongioblastoma unipolare showing the wirelike cell processes of the tumor cells.

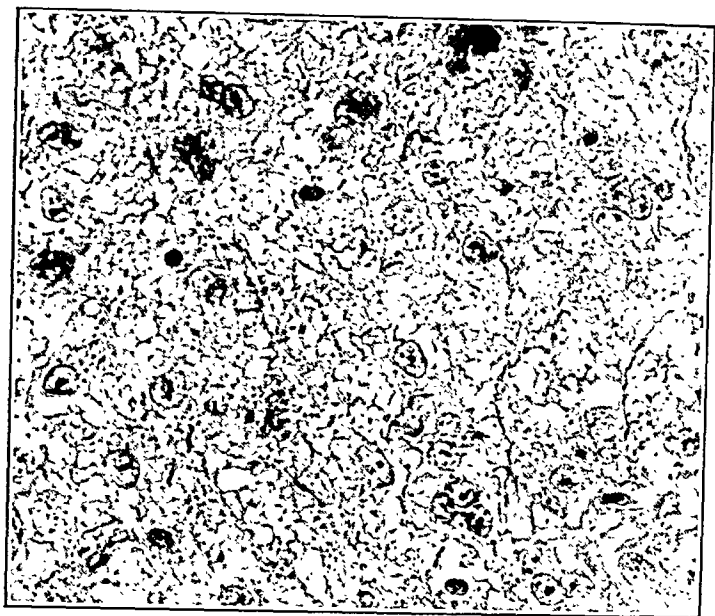


FIG. 12.—Section of a fibrillary astrocytoma showing the nuclei resting in a glial network.

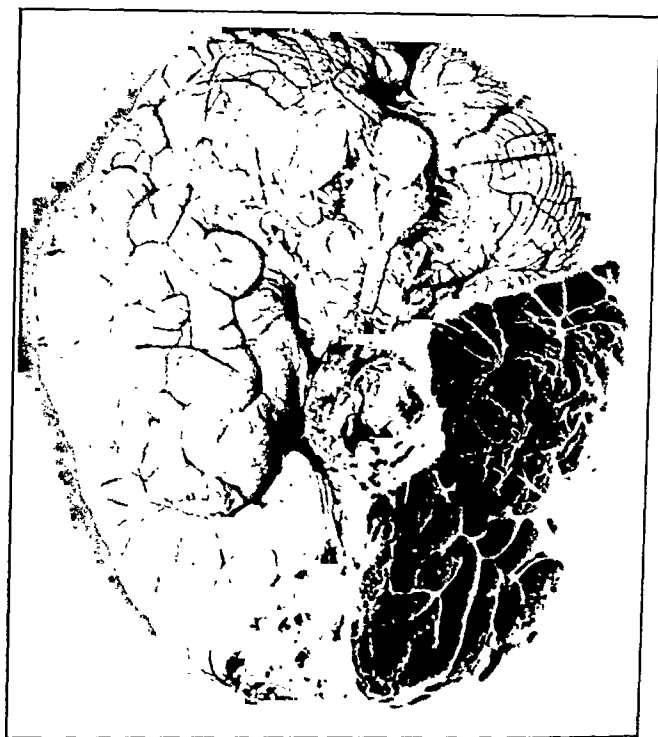


FIG. 13.—Rathke pouch tumor occurring in a young man 25 years of age.

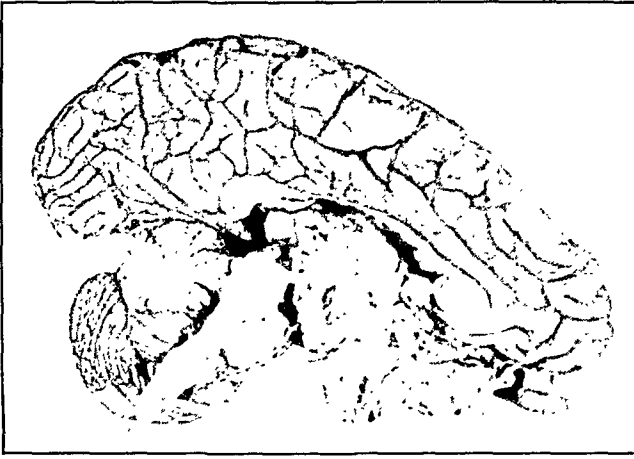


FIG. 14.—A large adamantinoma found in a girl 7 years of age.

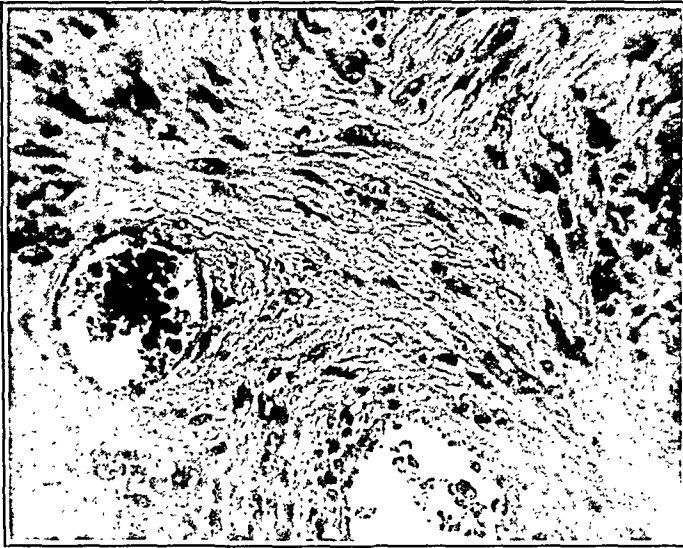


FIG. 15.—Interlacing bundles of connective tissue bands found in an acoustic perineurial fibroblastoma.

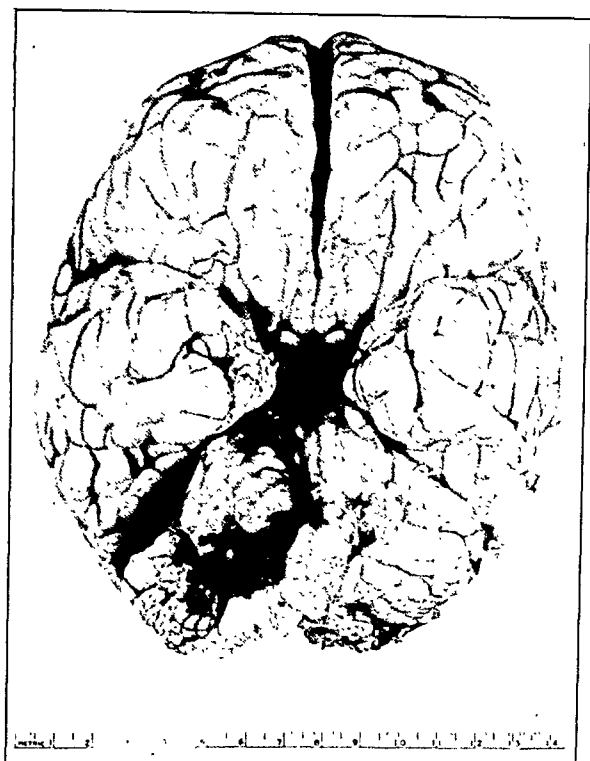


FIG. 16.—An acoustic perineurial fibroblastoma displacing the brain stem toward the opposite side.

dose of Roentgen ray directed on the tumor of each side of the head is given for a glioma of the hemisphere. The average duration of life in patients with these tumors is about $3\frac{1}{2}$ to 4 years.

(c) *Astrocytomata*. Over 40 per cent of gliomata are composed chiefly of astroblasts or protoplasmic and fibrillary astrocytes. These two types compose the pure gliomata. Astroblastomata are only relatively benign. They compose but a small percentage of astrocytomata. Roentgen ray therapy should be used with surgery, but definite benefit is doubtful. This group has an average survival period of about $2\frac{1}{2}$ years.

Protoplasmic astrocytomata are slow-growing, soft, relatively avascular tumors. These tumors may dedifferentiate and become more malignant, resembling a spongioblastoma multiforme. They are relatively benign, and the average survival of patients with this type of tumor is between 5 and 6 years. Intensive irradiation should follow surgery, for certain cases respond to this treatment.

Fibrillary astrocytomata (Fig. 12) are composed of the most highly differentiated cells. These tumors usually are found in middle life, but a certain number are found in the cerebellum of patients in the first and second decades. When exploration in these cases reveals a thick-walled cyst filled with yellow fluid a search should be made for a mural nodule of tumor.¹⁰ This must be removed or symptoms will soon recur. These tumors are the slowest growing, the most benign and the most resistant to irradiation. The average survival period is well over 6 years. Recurrence of symptoms is usually due to refilling of a cyst or to blockage of cerebrospinal fluid circulation. It is often necessary to operate again on the cystic tumors if the mural nodule of tumor is not identified and removed at the first operation.

3. PITUITARY TUMORS. Pituitary adenomata compose about 70 per cent of the tumors occurring in the region of the sella and about 5 per cent of all tumors of the brain. They may be composed chiefly of neutrophilic (also called chromophobe), acidophilic or basophilic cells. The two well-known varieties of pituitary adenomata composed of chromophil or chromophobe cells have definite constitutional manifestations apart from the local or pressure effects of the tumor which may call for surgical relief. Chromophobe adenomata may be associated with hypopituitarism, while the chromophil adenomata accompany the syndrome of acromegaly or hyperpituitarism. In the Lakeside Hospital a basophilic adenoma has been found in a polyglandular patient in whom the secondary sex characteristics were overdeveloped.^{10a} Frazier¹¹ has recently advocated glandular feedings of pituitary and thyroid extract for pituitary dysfunction without pressure phenomena. About 80 per cent of pituitary adenomata are solid, while the remaining 20 per cent are cystic. Formerly surgery was advocated in all cases of pituitary tumor with symptoms of increased intracranial pressure,

also with symptoms due to local pressure, such as blindness, oculomotor palsy, pituitary headache and in cases of acromegaly. At the present time surgical intervention is resorted to when vision is threatened or the headaches are very severe.

Recently good results have been reported by Towne from Roentgen therapy when used for suspected solid adenomata of the anterior lobe which have enlarged or destroyed the sella.¹² These treatments are to be followed closely by perimetric examinations. Roentgen ray treatments may be safely tried 6 months before surgery if there is no loss in the visual fields. Relief is usually not obtained under 6 weeks to several months. A cystic tumor is suspected in cases which do not respond to Roentgen ray therapy and these must be treated surgically. At the Lakeside Hospital a divided erythema dose of Roentgen ray is given to each side of the head, directed upon the sella. Some advocate intensive treatment to the front, top and back of the head in addition to the above method.

Nearly 20 per cent of tumors about the sella are craniopharyngeal pouch or Rathke's pouch tumors. (Fig. 13.) From such pharyngeal rests most unusual forms of neoplasm infrequently develop such as adamantinoma. (Fig. 14.) These congenital tumors arise from the pharyngeal pouch which forms the anterior lobe of the pituitary gland. They usually occur within the first or second decade of life. In young patients a picture of dyspituitarism is usually seen, consisting of nondevelopment of the sexual organs, dwarfism and a lowered basal metabolic rate. Mentally the patients are alert and even precocious. About 70 per cent show suprasellar calcification by Roentgen ray.¹³ (Fig. 3.) Treatment consists of aspirating the cyst by a transfrontal approach to save eyesight. These tumors do not respond to Roentgen ray therapy.

4. PERINEURIAL FIBROBLASTOMATA. These tumors are also known as acoustic neuromata, or spinal nerve tumors, and are said to compose about 6 per cent of all tumors of the brain.¹⁴ The patients usually give such a classic history that the correct diagnosis can be made in about 90 per cent of the cases. The Roentgen ray gives additional confirmation in a few cases. The pure perineurial fibroblastomata arise from the perineurium or endoneurium surrounding the nerve fasciculi.¹⁵ (Fig. 15.) They are usually attached to the cranial or spinal nerve roots. (Fig. 16.) In the cranial group the left acoustic nerve for some unknown reason is most often involved. The first and fifth cranial nerve roots are the next most common sites for these tumors. The nerve fibers are found passing around these tumors and not through them. In von Recklinghausen's neurofibromatosis bilateral involvement of the vestibular portion of the eighth nerve is not uncommon. In certain cases this may be the only manifestation of the disease. The histologic picture varies from that of the pure perineurial fibroblastoma. Nerve fibers pass through the tumor in von Reckling-

hausen's disease, but local areas may be found in these tumors identical with perineurial fibroblastomata. These tumors are very slow growing and do not respond to Roentgen ray therapy. They are in a difficult place to obtain exposure sufficient for complete removal. Again electrosurgery has made it possible to remove more of these tumors with greater ease and safety through the suboccipital approach. Surgery usually prolongs the life of these patients from 3 to 6 years, and in many cases the tumor may be completely removed.

Conclusions. There are several reasons for surgical intervention in cases of tumor of the brain. Regardless of the pre-operative pathologic diagnosis, exploration may reveal a lesion which is amenable to radical surgical treatment. Lesions which are amenable to surgery are meningiomata, certain acoustic neuromata and astrocytomata. At operation it is hoped to confirm the presence of a tumor and more accurately to localize it. If a specimen for histologic study is obtained the future course of the patient will be better understood and Roentgen ray therapy can be more accurately given. The prognosis in patients with gliomata can be made fairly accurately as to time and subsequent course only by histologic study. A decompression is usually done at the time of the exploration and this provides a safety valve which will take care of a reactionary edema or even hemorrhage into the tumor resulting from Roentgen ray therapy.

Roentgen ray therapy should be combined with surgery in the treatment of gliomata. The more embryonic the predominate type of cell in the tumor, the more effective this form of treatment will be. Cystic tumors of the pituitary should be treated surgically, while many solid adenomata of the anterior lobe of the pituitary may be controlled by Roentgen ray therapy alone.

REFERENCES.

1. Sosman, Merrill C., and Putnam, Tracy Jackson: *Am. J. Roentgenol.*, 1925, 13, 1.
2. Schreiber, F.: *Am. J. Roentgenol.*, 1930, 23, 607.
3. Camp, John D.: *Am. J. Roentgenol.*, 1930, 23, 615.
4. Frazier, C. H.: *Proc. Internat. Assembly Inter-State Post-Grad. Med. Assn., North America* (1929), 1930, 9, 5.
5. Bailey, Percival, and Bucy, Paul, C.: *Am. J. Cancer*, 1931, 15, 15.
6. Davidoff, L. M., and Ferraro, A.: *Am. J. Psychiat.*, 1929, 8, 599.
7. Bailey, Percival, and Cushing, Harvey: Philadelphia, J. B. Lippincott Company, 1926.
8. Cutler, Elliott C., Moritz, A. R., and Zollinger, R.: *Ohio State Med. J.*, 1929, 25, 269.
9. Penfield, W.: *Brit. Med. J.*, 1931, 1, 337.
10. Cushing, Harvey: *Surg., Gynec., Obst.*, 1931, 52, 129.
- 10a. Teel, Harold M.: *Arch. Neurol. and Psychiat.*, 1931, 26, 593.
11. Frazier, Charles: *Surg., Gynec. Obst.*, 1931, 52, 1069.
12. Towne, E. B.: *Arch. Neurol. and Psychiat.*, 1926, 15, 92; *Ann. Surg.*, 1930, 91, 29.
13. McKenzie, K. G., and Sosman, M. C.: *Am. J. Roentgenol.*, 1924, 11, 171.
14. Cushing, Harvey: Philadelphia, W. B. Saunders Company, 1917.
15. Penfield, W.: *Surg., Gynec. Obst.*, 1927, 45, 178.

ENDOCRINE THERAPY IN THE PSYCHOSES.*

By R. G. HOSKINS, PH.D., M.D.,

DIRECTOR OF RESEARCH, THE MEMORIAL FOUNDATION FOR NEURO-ENDOCRINE
RESEARCH, HARVARD MEDICAL SCHOOL, BOSTON,

AND

F. H. SLEEPER, M.D.,

RESIDENT DIRECTOR OF RESEARCH, THE WORCESTER STATE HOSPITAL, WORCESTER.

THE psychoses presents a problem in medicine, the magnitude of which is commonly much underestimated. In 1930 the average number of occupied hospital beds in the United States was about 736,000. Of these, well over half, or about 419,000, were occupied by victims of nervous and mental disorders. Of these, in turn, the the great majority were frankly psychotic. Schizophrenia, or dementia præcox, alone furnished the occupants for one-fifth of all occupied beds. The economic cost of the disorder in this country is well over \$1,000,000 a day. The social cost cannot be calculated: The disorder characteristically takes onset in the early prime of life and runs through a life span that is not greatly shortened; each case represents a wrecked life and a grave social maladjustment. This psychosis, then, presents the outstanding medical problem of today. Since it has been most adequately studied, this discussion will deal primarily with schizophrenia, but with incidental attention to some of the other psychoses.

Whether schizophrenia is fundamentally of psychogenic or of organic origin has been long and rather unprofitably debated. That emotional stresses play a large part in precipitating the disorder cannot be questioned. The burden of the evidence, however, indicates rather conclusively that it is dependent also upon a constitutional liability factor. It shows a predilection for individuals with tainted heredity and of dysplastic constitutional types. The most convincing datum is the high incidence of double involvement in monozygotic as compared with ordinary fraternal twins.¹ These characteristics are most plausibly explicable on the assumption that the disorder arises only in those organically liable to it.

Much thought and more than a little research have gone into an attempt to identify the underlying liability factor or factors. A large body of respectable opinion holds that the subjects are victims of some sort of vague metabolic disorder amounting to a chronic intoxication. This, in turn, might well depend directly or indirectly upon abnormal endocrine functions.

The question arises whether, as a matter of fact, endocrine abnormalities can be demonstrated as a common factor in the psychosis.

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If not, endocrine therapy would presumably offer little hope. Three lines of evidence in this connection demand consideration. Is there a significantly high incidence among schizophrenics of the morphologic stigmata of endocrine abnormalities? Are the physiologic and metabolic functions distorted as they are in endocrine disorders? Do the endocrine glands of the psychotic subjects themselves show characteristic pathologic changes?

Morphologic Stigmata. Wertham² has recently reported a study of bodily abnormalities in 923 unselected psychiatric patients. He considered skeletal abnormalities, lack of symmetry, bodily disproportions and malformations, anomalies of primary and secondary sex characteristics, of fat distribution, of hair distribution and complexion. More than a third of his schizophrenic group showed such disorders. A similar high incidence of constitutional abnormalities has been reported by Raphael, Ferguson and Searle,³ by Schmidt⁴ and by Kretschmer.⁵ Abnormalities in the sex field are especially common in schizophrenia as they are in demonstrated endocrine dysfunctions. Too, there is a high incidence of the so-called "thymolymphatic constitution," a condition marked by scanty beard, axillary and sternal hair; slender thorax; rounded contour of the upper arms and thighs; genital hypoplasia and velvety skin. These constitutional deviations are interpreted by most students as due primarily to glandular abnormalities. The outstanding evidence was reviewed by Hoskins⁶ in 1929.

Physiologic and Metabolic Disturbances. Perhaps the most characteristic single finding in endocrine deficiency is depression of the basal metabolic rate. There are now available in the literature reports on approximately 300 cases of schizophrenia that include data on this topic (Fischer⁷ and Hoskins and Sleeper⁸). These reports sufficiently demonstrate that the disorder is characterized by a systematic depression of over 10 per cent. Fischer has noted, too, a characteristic depression of the specific dynamic action of food, suggesting to him pituitary deficiency as the outstanding etiologic factor. These depressions are commonly noted in patients in whom no intercurrent physical disorders can be detected to account for the deviations and constitute substantial presumptive evidence of endocrine deficiency. The sugar metabolism likewise is rather commonly abnormal. The literature on this point was reviewed by the authors in 1930.⁹ The blood pressure is depressed on the average about 10 per cent. The literature on this point has recently been compiled by Freeman, Hoskins and Sleeper,¹⁰ who have added studies on 180 cases. The disorder is characterized by a great variety of other perturbations throughout the domain of the autonomic nervous system. These include cyanosis of the extremities, dermatographism, inequality and irregularities of the pupils and sweating. Low body temperature and fatigability are likewise common findings.

On the whole, the metabolic and functional characteristics of the psychosis are strongly suggestive of endocrine deficiencies. Granted technical competence the metabolic deviations could probably all be reproduced by creating suitable glandular abnormalities. On the other hand, the defects might conceivably be accounted for, in part, at least, by chronic emotional disturbances.

Endocrine Pathology. There is a fairly large body of literature indicating a high incidence of structural defects in the endocrine glands in case of schizophrenia and to a less extent in case of other psychoses. Deficiencies in the sex glands are especially frequently reported. Cushing¹¹ has stated that he failed to find a single normal pituitary in 70 State Hospital cases. Abnormal thyroids, too, have been frequently reported, regressive signs being especially common. On the whole, it may be said that fairly extensive changes, generally of a degenerative nature, are commonly found in the endocrine glands of the schizophrenics. Whether, however, these changes are characteristic of the psychosis as such, or whether they are incidental to age, or to the intercurrent diseases or nutritional state of the patients, the existing evidence fails to prove. As a matter of fact, there are practically no studies in the literature based on adequate cytologic technique and with suitable control material. Until such studies are made in sufficient number to permit valid statistical analysis we shall presumably remain in the dark as to whether structural endocrine abnormalities are a consistent part of the picture.

Personality Changes and Gland Defects. Direct evidence that endocrine deficiencies can produce striking personality deviations can be cited in considerable amount. McLester¹² has described a clinical picture of general "poor health" due to thyroid deficiency and marked by chronic nervous exhaustion, impairment of the reasoning power, incapacity for mental effort and lack of initiative. Such patients are definitely benefited by thyroid treatment. Wagner-Jauregg¹³ recognizes a prepsychotic type of personality associated with hypoplastic constitution due to combined ovarian and thyroid deficiency. This type is likely to develop hebephrenia, but may go through life merely showing futile personality. In either case, the author believes combined thyroid-gonad medication to be beneficial. Schrijver-Hertzgera and Schrijver¹⁴ reported a notably careful study of a peculiar case of "degenerative psychosis" with schizoid, cyclothymic and hysteric features and periodic attacks of confusion. In the features of late maturity, obesity, sterility and various metabolic findings the physical status suggested thyroid deficiency. Prolonged study proved the unequivocal beneficial effect of thyroid medication. It is a matter of textbook knowledge that high grades of thyroid deficiency result in general sluggishness, dulling of the sensibility, retardation of thinking as well as motor activity. The mood is not infrequently depressed, and in severe

cases illusions and hallucinations of hearing, sight, smell and taste and even compulsive states occur. Lawrence and Rowe¹⁵ have specifically recognized another variety of hypothyroidism, "the thin, irritable type," in which the subjects, far from being sluggish, are pathologically overresponsive to environmental annoyances. These patients promptly normalize under thyroid medication. Santenoi¹⁶ has published voluminous experimental evidence that cerebral functions are markedly affected by variations in the amount of thyroid hormone in the circulation.

That the gonads play an important rôle in determining personality has been believed from time immemorial. Castration is commonly regarded as calamitous. Certainly in the lower animals, and probably often in man, deprivation of the testicular secretion results in a loss of those characteristics connoted by the term virile. Ovarian deficiency of women often results in fatigue, general weakness, headache, irritability and depression. In Rowe's¹⁷ graphic terms, "an insistent expressed egoism is the keynote of the hypogonad character. Coupled with and dependent on this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies. Hyperemotionalism and self-pity are united with an attitude of acrid criticism of environmental conditions that are always unsatisfactory. The psychologic study of the average woman suffering from ovarian insufficiency would be a profitable but scarcely a pleasant task." The occasional occurrence of profound melancholia at the climacteric period in both men and women is another datum suggestive of the importance of the gonad secretions in maintaining normal psychic life.

The recent demonstration of the determining influence of the anterior lobe of the pituitary on the sex functions suggests that this gland, too, may be involved in the aforementioned manifestations of gonad deficiency. The administration of the sex-stimulating fraction of anterior pituitary extracts has definitely been shown to exercise an erotizing effect in immature or castrated animals. Tucker¹⁸ has described a condition of "pituitary psychosis" that in his opinion derives from deficient secretion of this gland and can be ameliorated by pituitary medication. The psychosis resembles dementia præcox but marked hysteria may also be evident.

The parathyroids, too, are well known to have an important influence on nervous activities. Parathyroid deficiency has often been shown to result in tenseness that may extend even to clonic convulsions. Clouding of consciousness is occasionally noted and a considerable number of outspoken psychoses have been reported with hallucinatory confusion and mood disturbances. In chronic parathyroid tetany mental dullness and enfeeblement are not uncommon. Looney¹⁹ has reported some success in the control of the rigidity of catatonic dementia præcox patients by the use of parathyroid extracts. Bowman²⁰ and the present writers have

failed to demonstrate any very significant clinical effects from such medication. Timme²¹ has recognized a peculiar behavior disorder that is apparently correlated with parathyroid deficiency. The patients showed incorrigibility, unamenability to discipline and assaultiveness. A trifling provocation sufficed to arouse intense anger. In several instances the condition progressed to a hypomania that demanded institutional treatment. Under parathyroid extract supplemented by calcium and sunlight the tenseness, myotatic irritability and conduct disorders rapidly improved.

That other endocrine organs have more or less definite influence on the higher nervous functions is altogether probable, but the unequivocal evidence is too scanty to warrant more than casual mention. Pineal tumors are at times associated with mental as well as physical precocity. Deficiency of the thymus has been reported as common in mentally deficient children. The general lassitude characteristic of adrenal deficiency no doubt repercusses significantly in the mental sphere. The terminal delirium of Addison's disease demonstrates a relationship if only secondarily and as an expression of toxemia.

Altogether, there can be no doubt that endocrine deficiencies play an important part in determining the functional capacity of the higher nervous system. The probability that the psychoses are significantly correlated with such deficiencies accordingly possesses a probability little short of certainty. There can be no doubt, then, that the problem of the psychoses justifies an exhaustive experimental endocrine therapeutic approach. Ideally, however, gland therapy should be prescribed only for patients in whom adequate diagnostic studies have disclosed specific indications. It is not surprising that in view of the well-known lag in the development of diagnostic methodology in this field a great deal of random endocrine therapy has been practised.

As would be expected under such circumstances, numerous failures have resulted among psychotic as they have among nonpsychotic patients. More than 20 years ago Kraepelin²² wrote: "Many years ago I endeavored to acquire influence on dementia præcox by the introduction of every possible organ, of the thyroid gland, of the testes, of the ovaries, and so on, unfortunately without any effect." In this, as in all similar cases, however, the question still remains open. Negative evidence is conclusive only when it is shown that a preparation of the gland appropriate for the individual patient was selected; that a potent product was used, that the dosage was adequate and that the treatment was continued for a sufficient period. We know of few reports of negative results in which these criteria have been met.

Until recently, therapists have been sadly handicapped by the lack of potent gland preparations. Such hope as there may be in the endocrine treatment of the psychoses has been and is being

rapidly improved by successful world-wide researches on the chemistry and pharmacology of the glands.

Endocrine Therapy. In the actual successful endocrine treatment of psychotics the palm would seem to go to Lewis and Davies.²³ From the wards of St. Elizabeth's Hospital they selected for treatment 20 schizophrenics, and in all cases definite physical or mental improvement, concurred in by 6 observers, was obtained. Four made sufficient mental improvement to be discharged and 9 others partly recovered.

Kauders²⁴ has reported a study on the efficacy of male and female gonad extracts. He concludes that treatment must be extended over months and that from 15 to 20 times the usual indicated dosage must be used. He reports specifically on the treatment of 8 male schizophrenics who had been getting progressively worse for years. One paranoid and 1 catatonic subject showed noticeable improvement after the first 3 weeks, 1 finally being completely cured. One subject, for 2 years in stupor, after the third month's treatment showed no psychotic symptoms except negativism. Another, paranoid, for 3 years, corrected his delusions after 3 months' treatment and showed general improvement. The other 4 patients had shown no mental improvement, but 2 were improving physically. Similarly favorable results from testis extracts, especially in cases of early onset, have been reported by Keresztes.²⁵ Sippel²⁶ has reported uniformly successful results in 6 patients into whom healthy ovarian tissue was transplanted. Bentley²⁷ reported strikingly favorable results in chronic cases following the administration of a mixture of thyroid, gonad and pituitary substance.

Mayer²⁸ reported the case of a rather typical catatonic who, under thyroid treatment, went through a manic phase, then became free from mental symptoms. Davidson²⁹ also reported a single case successfully treated with thyroid substance in increasing doses up to 60 grains daily.

Hübner reported good results from thyroid medication in a few cases, but since he noted an equally favorable influence from anti-thyreoidin his evidence is equivocal. Sawkins³¹ reported an illustrative single case of a man, past 50 years of age, a hospital inmate for 20 years; he was an idle, pestilential, petty thief and fomenter of discord, who spent most of his time in the refractory ward. After reaching 75 grains a day (probably in terms of fresh gland) the thyroid was gradually reduced to 5 grains. In the latter stage of the treatment the patient's weight and vitality increased, his conversation became sensible and in a few months he became notably trustworthy. He was ultimately discharged and for the past few years had been self-sustaining.

During the current year Hayward and Woods³² have again emphasized the importance of thyroid deficiency as a factor in the malfunctioning of the brain cells. Their experience coincides with

that of previous authors in showing that thyroid deficiency may result in either a depressed psychosis or in irritability and excitement leading to the diagnosis of mania. The patients may show thought distortion with hallucinations and delusions which may become so bizarre as to be interpreted as signs of dementia præcox. They reported a case of frank psychosis with schizoid coloring in a woman, aged 41 years, who showed various metabolic evidences of thyroid deficiency. Under thyroid medication the psychosis completely cleared up.

For the past 4 years we have been engaged in a somewhat elaborate diagnostic and therapeutic investigation of the schizophrenia problem at the Worcester State Hospital. So many are the variables in the problem, however, and so difficult is adequate control that few final conclusions are yet possible.

The characteristic metabolic picture in schizophrenia is strongly suggestive of suprarenal cortex deficiency as a common underlying feature. With the suprarenal preparations, however, that have been available to us no significant amelioration of the psychosis—nor, indeed, any significant influence on the metabolic functions—have been recognized. A study on 9 cases has recently been reported.³³ Similarly, we have obtained negative results with a glycerin extract of bovine testes. The results with pituitary preparations have been equivocal, but there is a suggestion of a beneficial effect that demands a careful statistical analysis of our data.

Last year we reported a "first approximation" of results secured with thyroid therapy.³⁴ Among 130 subjects of dementia præcox a group of 18 was diagnosed as suffering from thyroid deficiency. Of these, 16 received thyroid treatment. Significant mental improvement followed in 14, or 88 per cent, of the cases, and 5 patients had become well enough to go home. A control group of 41 patients in whom definite thyroid deficiency could not be recognized but who had received similar thyroid treatment was available. The incidence of significant improvement in this group was only 34 per cent. Since 31 of the group were recorded as showing "endocrine deficiency unclassified," it is probable that some of these subjects, too, suffered from some degree of thyroid deficiency, a fact that may account for some of the improvement noted. Also, a considerable number of the control subjects had received other types of medication and this, too, may have contributed somewhat to the improvement. Here, as in all cases, however, a troublesome factor, namely, "spontaneous variability," no doubt intruded. The contrast between 88 per cent of hypothyroid patients showing improvement under this medication with 34 per cent of the control group not demonstrably hypothyroid was offered as evidence of a specific therapeutic effect. Since the series was made up almost entirely of cases having an ominous prognosis, the beneficial effects seemed to possess an added significance. The results were interpreted as indicating that thyroid deficiency plays a significant rôle in more

than 10 per cent of hospitalized cases of dementia præcox, and that in properly selected cases thyroid medication in adequate dosage and for a sufficiently prolonged period results in significant improvement. On the other hand, relatively little success is to be anticipated from thyroid medication in cases selected at random. A striking feature of our data is an indication that the threshold for thyroid medication in this disorder is frequently surprisingly high, and that relatively very large doses can be safely administered or, indeed, must be administered to secure significant therapeutic results. Further studies since the publication of the data reported suggest that upon discontinuance of the thyroid therapy the improvement is likely to be lost. Likewise, there is a suggestion that there are often other etiologic factors operative even in the hypothyroid subjects and that these, too, must be corrected before complete success can be achieved. No final conclusions can be drawn until many more studies have been made and the data subjected to rigid statistical analysis to determine the relative weights of the presumably numerous factors involved in the equation.

A major difficulty in such studies is the looseness of the term schizophrenia itself. It is not unlikely that the disorder comprises a variety of distinct affections just as the term fever may denote pneumonia, arthritis, starvation, dehydration or what not. Before finally conclusive results can be anticipated in either diagnostic or therapeutic studies it will probably be necessary to determine much more specifically the component varieties of the psychosis.

Summary. It may be said that in all probability the psychoses are influenced in a variety of ways by the endocrine status of the subjects. There is abundant justification for elaborate and long-continued diagnostic and therapeutic studies of the significance of endocrine factors. Successful results from endocrine medication in a variety of cases have been reported, but, in general, control studies have been inadequate or totally lacking. The importance of the psychoses among the acute medical problems of the day has been commonly underestimated. Research in psychiatry now lags far behind that in organic medicine. The number of hospitalized cases of different disorders can be taken as a rough indicator of the need for research in each. If this be granted, it must be conceded that not until the mental and nervous disorders are receiving as much attention as all other diseases combined will a proportionately fair allocation of effort have been achieved.

BIBLIOGRAPHY.

1. Lange, J.: Zwillingspathologische Probleme der Schizophrenie, Wien. klin. Wchnschr., 1929, 42, 1213. See also, Parker, G. H., Dementia Præcox in Identical Twins, J. Nerv. and Ment. Dis., 1926, 63, 135.
2. Wertham, F. I.: The Incidence of Growth Disorders in 923 Cases of Mental Disease, Arch. Neurol. and Psychiat., 1929, 21, 1128.
3. Raphael, T., Ferguson, W. G., and Searle, O. M.: Constitutional Factors in Schizophrenia, In "Schizophrenia (Dementia Præcox)," 1928, Paul B. Hoeber, Inc., New York, p. 100.

4. Schmidt, N.: Körperbau und Geisteskrankheit. Eine anthropologisch-klinische Untersuchung zur Beleuchtung des psychiatrischen Konstitutionsproblems, Julius Springer, Berlin, 1929.
5. Kretschmer, E.: Keimdrüsenfunktion und Seelenstörung, Deutsch. med. Wchnschr., 1921, 47, 549.
6. Hoskins, R. G.: Endocrine Factors in Dementia Præcox, New England J. Med., 1929, 200, 361.
7. Fischer, S.: Gasstoffwechseleränderungen bei Schizophrenen (I Mitteilung) Differentialdiagnostische Bedeutung, Klin. Wchnschr., 1927, 6, 1987. Gasstoffwechseleränderungen bei Schizophrenen, Arch. f. Psychiat., 1928, 83, 205.
8. Hoskins, R. G., and Sleeper, F. H.: Basal Metabolism in Schizophrenia, Arch. Neurol. and Psychiat., 1929, 21, 887.
9. Sleeper, F. H., and Hoskins, R. G.: Galactose Tolerance in Dementia Præcox, Arch. Neurol. and Psychiat., 1930, 24, 559.
10. Freeman, H., Hoskins, R. G., and Sleeper, F. H.: The Blood Pressure in Schizophrenia. Arch. Neurol. and Psychiat., 1932, 27, 333.
11. Cushing, H.: Psychic Disturbances Associated With Disorders of the Ductless Glands, Am. J. Insan., 1912-1913, 69, 964.
12. McLester, J. S.: Thyroid Deficiency as a Cause of Poor Health, Med. Clin. North America, 1929, 12, 1357.
13. Wagner-Jauregg: Organotherapie bei Neurosen und Psychosen, Wien, klin. Wchnschr., 1923, 36, 1.
14. Schrijver-Hertzgera, S., and Schrijver, D.: Körperliche Erscheinungen in einem Fall von episodischen Verwirrheitszuständen, Ztschr. f. d. ges. Neurol. u. Psychiat., 1930, 125, 388.
15. Lawrence, C. H., and Rowe, A. W.: Studies of the Endocrine Glands. III. The Thyroid, Endocrinology, 1928, 12, 377.
16. Santenoi, D.: Pneumogastrique, Appariel Thyroïdien et Activité Cérébrale, A. Legrand, Paris, 1929.
17. Rowe, A. W., and Lawrence, C. H.: Study of the Endocrine Glands. IV. The Male and Female Gonads, Endocrinology, 1928, 12, 591.
18. Tucker, B.: Pituitary Disturbance in Its Relation to the Psychoses of Adolescence, J. Am. Med. Assn., 1918, 71, 330.
19. Looney, J. M.: The Control of the Muscular Rigidity of Catatonic Precox Patients by Parathyroid Hormone, J. Biol. Chem., 1926, 67, 37.
20. Bowman, K. M.: Parathyroid Therapy in Schizophrenia, J. Nerv. and Ment. Dis., 1929, 70, 353.
21. Timme, W.: Pluriglandular Syndrome Involving Calcium Deficiency and Correlated With Behavior Disturbances, Arch. Neurol. and Psychiat., 1929, 21, 254.
22. Kraepelin, E.: Dementia Præcox and Paraphrenia. Translated by R. Mary Barclay, Ed. G. M. Robertson, Chicago Med. Book Company, 1919.
23. Lewis, N. D. C., and Davies, Gertrude R.: A Correlative Study of Endocrine Imbalance and Mental Disease, J. Nerv. and Ment. Dis., 1921, 54, 385; 1922, 55, 13.
24. Kauders, O.: Neue Erfahrungen und Ausblicke zur Organotherapie der Dementia Præcox. Allg. Ztschr. f. Psychiat., 1926, 83, 408.
25. Keresztes, G.: Hormone Treatment of Schizophrenia, Gyógyászat., 1927, 67, 719. (In Hungarian) Abst., Endokrinologie, 1928, 2, 449.
26. Sippel, P.: Die homoplastische Ovarientransplantation bei Schizophrenie, Klin. Wchnschr., 1926, 4, 401; Abst. J. Nerv. and Ment. Dis., 1929, 70, 448.
27. Bentley, J.: Some Illustrative Cases of Ductless Gland Therapy in the Insane Med. J. Australia, 1921, 1, 399.
28. Mayer, W.: Ueber Psychose bei Störung der inneren Sekretion, Ztschr. f. d. ges. Neurol. u. Psychiat., 1914, 22, 477.
29. Davidson, A.: A Case Illustrating the Use of Thyroid Extract in Dementia Præcox, Australasia Med. Gaz., 1912, 30, 200.
30. Hübner, A.: Ueber therapeutische Versuche bei Dementia Præcox, Neurol. Centralbl., 1919, 38, 636.
31. Sawkins, F. J. T.: Some Notes on Thyroid Therapy, Med. J. Australia, 1924, 2, 677.
32. Hayward, E. P., and Woods, A. H.: Mental Derangements in Hypothyroidism. Their Misleading Effects in Diagnosis, J. Am. Med. Assn., 1931, 97, 164.
33. Hoskins, R. G., and Sleeper, F. H.: A Metabolic Study of Desiccated Suprarenal Medication in Man, Endocrinology, 1930, 14, 109.
34. Hoskins, R. G., and Sleeper, F. H.: The Thyroid Factor in Dementia Præcox, Am. J. Psychiat., 1930, 10, 411.

WHITE BLOOD CELL COUNTS IN CONVALESCENCE FROM INFECTIOUS DISEASES.*

BY PAUL REZNIKOFF, M.D.,

INSTRUCTOR OF MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE; ASSOCIATE
VISITING PHYSICIAN, SECOND MEDICAL (CORNELL) DIVISION, BELLEVUE
HOSPITAL, NEW YORK CITY.

(From the Department of Medicine, Cornell University Medical College, the Second
Medical (Cornell) Division, Bellevue Hospital, and the First Medical Clinic,
Charitékrankenhaus, Berlin, Germany (Geheimrat His, Director).)

THE Schilling¹ hemogram is of distinct value in a study of acute infections. It is probably the most delicate index of severity of illness, prognosis and imminence of complications which the laboratory can offer.² However, the help of the laboratory, as far as blood counts are concerned, is frequently just added information. The clinician, as a rule, can tell when a patient is acutely ill. In a typical acute infection like lobar pneumonia the appearance and complaints of the subject, the physical signs which can be elicited, and the temperature, pulse and respirations offer a definite picture which indicates that a person is sick. It is much more difficult to determine when a patient is well, and it is during recovery and convalescence that the hemogram can be of decided help. Most physicians and hospitals have a routine in gauging convalescence. In acute lobar pneumonia a patient is usually permitted to leave his bed after his temperature has been normal for 10 days. After an attack of grippe many patients are no longer confined to bed after four days of normal temperature. In such diseases as acute rheumatic fever bed care is much more variable, but judging from the frequency of complications and recurrences no definite idea is prevalent among physicians as to when the phase of convalescence has ended and that of recovery begun. Swift³ emphasizes the need for convalescent care in rheumatic fever long after the symptoms and signs of the acute disease have disappeared. This indicates how unreliable the patients' symptoms and signs are in this condition as evidence of recovery.

It is obvious that no two patients are alike in illness or in recovery from illness and that a blanket rule of a given number of days of convalescent bed care may be insufficient for some patients and too much for others. It is a common experience that a certain number of patients feel in excellent condition after leaving their beds and others, after an apparently similar illness and similar convalescent course, feel decidedly below par.

* This report was made possible through the courtesy of Prof. Victor Schilling, under whose direction the author worked for part of this study.

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At the suggestion of Prof. Victor Schilling, a study was undertaken to see if, in patients suffering from various acute infections, some information could be obtained from the hemogram or Schilling index as to the progress of convalescence.

The technique used was similar to that employed in the previous study of the acute phase of infectious diseases.² Total white blood cell counts were made with standardized pipettes, as far as possible under Garrey's⁴ basal conditions at regular intervals. The Schilling counts were made from coverslips, stained with Wright's stain and prepared at the same time that the blood was drawn for white cell counts. Table 1 illustrates the values considered normal for the different cells in this work. Basophils are not given because they play no important part in this study. Between 6000 and 8000 is called a normal total count. Both percentages and absolute values were determined, but the latter were found to be of much less value than the percentage determinations because of the great variation of total count in different phases of pathologic conditions.

TABLE 1.—NORMAL VALUES OF CELLS (BASED ON ABOUT 250 CASES).

Immature polymorphonuclears:

	Per cent.	Total count. per. cu. mm.
Myelocytes		
Young forms		
Band forms	4-7	240-560
Mature polymorphonuclears	50-65	3000-5200
Lymphocytes	20-38 ^s	1200-3000
Monocytes	3-10	180-800
Eosinophils	0.5-3	30-240

About 200 patients were studied, a few on the wards of the First Medical Clinic of the Charitékrankenhaus, Berlin, and most on the wards and in the out-patient department of the Second Medical Division of Bellevue Hospital. The diseases followed were: pneumonia, rheumatic fever, infectious arthritis, acute tonsillitis, scarlet fever, erysipelas, cerebrospinal meningitis and lymphangitis.

All these patients showed minor variations in their counts, especially in the degree and duration of the rise of certain forms. Also various diseases presented somewhat different patterns. But in general, convalescence from all the infections studied produced hemograms which were remarkably constant.

During the active infection the hemogram shows an increase in immature polymorphonuclear cells ("shift to the left"), and a depression of lymphocytes, monocytes and eosinophils. These changes are both relative and absolute. As the intensity of the infection subsides there is a decrease in the number of immature polymorphonuclear cells and the monocytes increase abruptly. In some conditions like pneumonia this increase in monocytes may last a very short time, sometimes for only 24 hours. As convalescence progresses the immature polymorphonuclears return to normal, the monocytes decrease and the lymphocytes and eosinophils

increase. Complete recovery is usually accompanied by a return of the hemogram to normal.

There are many variations of this process. In some infections, such as infectious arthritis, the high monocyte phase may last a long time. In diseases like rheumatic fever, scarlet fever, tonsillitis and in a few patients with pneumonia the eosinophilic increase (from 5 to 17 per cent) may occur early in convalescence and recur late in convalescence or may persist a long time. The duration of the high lymphocyte count may vary markedly in individual cases. Moreover the various phases may overlap.

■ IMMATURE POLYS □ ADULT POLYS ▨ LYMPHOCYTES ▩ MONOCYTES ▤ EOSINOPHILES

CHART I.—Designation of various white blood cells in charts.

To obtain a clearer view of the hemogram in convalescence a few cases may be selected as illustrations. In the charts to be presented Chart I illustrates the manner of designating the various cells: Solid black represents immature polymorphonuclears; clear area, adult polymorphonuclears; diagonally lined, lymphocytes; stippled area, monocytes; horizontally lined, eosinophils. As mentioned previously, basophils were not included because they have no importance in this study. In some of the tables the total values are included as well as percentages, but as will be demonstrated in one of the charts (Chart V), the striking features of this study are evident, regardless of whether percentages or total counts are used.

In the first place, Chart II and the accompanying Table II show the course of hematologic events in an acute infection with fatal outcome.

Case Abstracts. CASE 1.—This patient (J. O'B.), in brief, was a male, aged 37 years, admitted with a history of a cough for 4 weeks and a sudden chill, cough and generalized pains 3 days before admission. His left upper lobe showed classical signs of consolidation and he died 6 days after his admission.

The chart shows that on admission his temperature was 105° F., and he had a marked increase in his immature polymorphonuclear cells (54 per cent), with a depression of his lymphocytes and monocytes (3 and 6 per cent respectively) and an absence of eosinophils. His condition improved in the next 3 days so that his temperature dropped to 101° F., his immature polymorphonuclears declined and there was a slight rise of his lymphocytes and a marked rise of his monocytes (18 per cent on January 13). But 2 days before his death (and the day before to a marked extent) there was a definite increase in his immature polymorphonuclears. On the day he died his immature polymorphonuclears numbered 67 per cent and his lymphocytes and monocytes were markedly depressed (4 per cent each), with a complete absence of eosinophils.

This case, therefore, illustrates the cardinal features of bad prognosis as far as the hemogram is concerned: increase of immature polymorphonuclears, decrease of lymphocytes, monocytes and absence or marked depression of eosinophils.

With this case in mind it may be of interest to study the results obtained in an individual who recovered from an attack of lobar pneumonia.

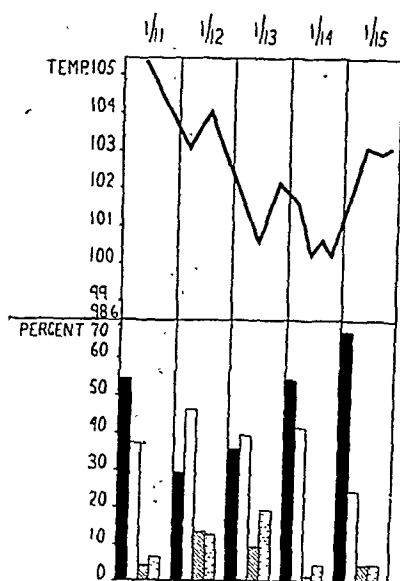


CHART II.—Hemogram of patient J. O'B., who died from lobar pneumonia.

TABLE 2.—HEMOGRAM OF CASE 1; DIED FROM LOBAR PNEUMONIA.*

Date.	W.B.C.	Immature polys.		Adult polys.		Lymphocytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1929											
Jan. 11 . .	7.5	54	4.1	37	2.8	3	.225	6	.450	0	0
12 . .	7.0	29	2.0	46	3.2	13	.900	12	.850	0	0
13 . .	7.6	35	2.7	39	2.9	8	.600	18	1.350	0	0
14 . .	11.0	54	5.9	41	4.5	1	.100	4	.450	0	0
15 . .	10.1	67	6.8	24	2.4	4	.400	4	.400	0	0

* In this and subsequent tables all white cell counts are recorded in thousands per cu. mm.

CASE 2.—The patient (S. K.), represented by Chart III and the accompanying Table 3, was admitted with the history of having had a chill 3 days before admission, complaining of general aches, nausea, vomiting, slight productive cough and having slight pain in his upper chest. Upon examination he had some polypnea, slight cyanosis, rusty sputum and he looked acutely ill. His throat was injected and over his right apex, down to the third rib, he showed dullness and diminished intensity of breath sounds. His expiratory sounds were bronchial in character, as was his whispered and spoken voice, and his fremitus was slightly increased. Numerous crepitant râles were heard on inspiration. A Roentgen ray plate showed engorgement of his entire right lung. Type II pneumococcus was recovered from his sputum.

The chart shows that on November 19 he had a marked relapse with rise of temperature to 103° F., an increase of immature polymorphonuclears to 49 per cent and a depression of lymphocytes (10 per cent), monocytes (5 per cent) and eosinophils (0 per cent). On the next day his monocytes began to rise and attained 17 per cent within 2 days, as his immature polymorphonuclears fell. As his convalescence progressed his lymphocytes and eosinophils began to increase in number. Unfortunately this patient left the hospital before his further course could be studied. But in patients who have been followed a lymphocyte count above 40 per cent persists often for weeks.

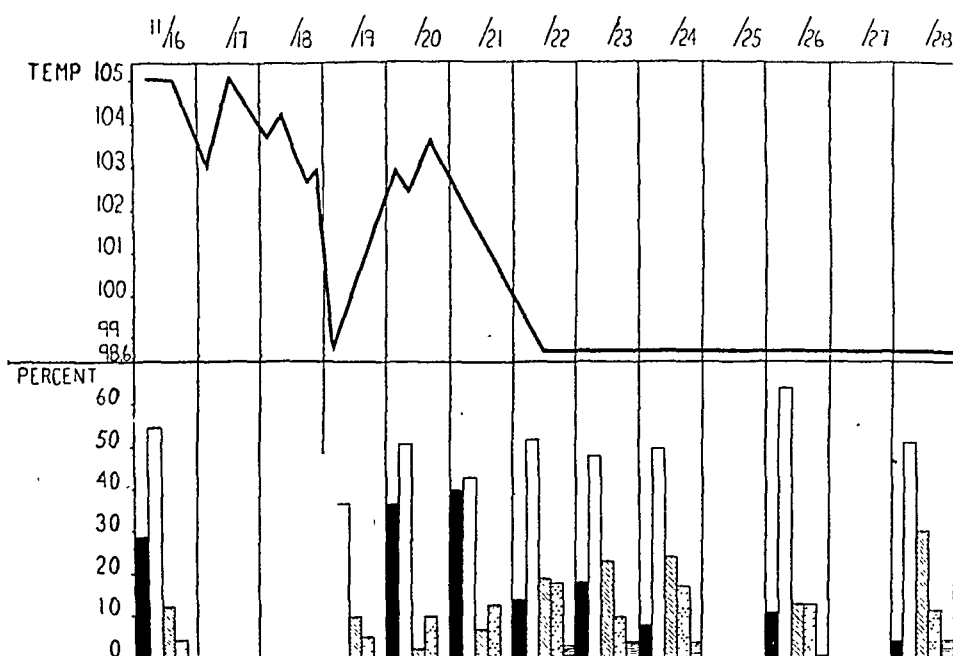


CHART III.—Hemogram of patient S. K., who recovered from lobar pneumonia.

TABLE 3.—HEMOGRAM OF CASE 2; RECOVERED FROM LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys.		Adult polys.		Lymphocytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
Nov. 16 . .	26.0	29	7.5	55	14.3	12	3.1	4	1.0	0	0
19 . .	18.3	49	9.0	36	6.6	10	1.8	5	.9	0	0
20 . .	31.0	37	11.5	51	15.8	2	.6	10	3.1	0	0
21 . .	32.8	40	13.1	42	13.8	6	2.0	12	3.9	0	0
22 . .	18.8	13	2.4	51	9.6	19	3.6	17	3.2	2	.375
23 . .	17.4	18	3.1	47	8.2	22	3.8	10	1.7	3	.525
24 . .	14.1	7	1.0	50	7.1	23	3.2	16	2.3	4	.550
26 . .	13.0	11	1.4	64	9.3	12	1.6	12	1.6	1	.125
28 . .	9.1	4	.35	51	4.6	30	2.7	11	1.0	4	.350

The next 3 cases illustrate one of the most interesting features of the hemogram, its meaning in complications.

CASE 3.—The first of these, shown by Chart IV and its accompanying Table 4, represents the findings in a woman (V. S.), aged 39 years,

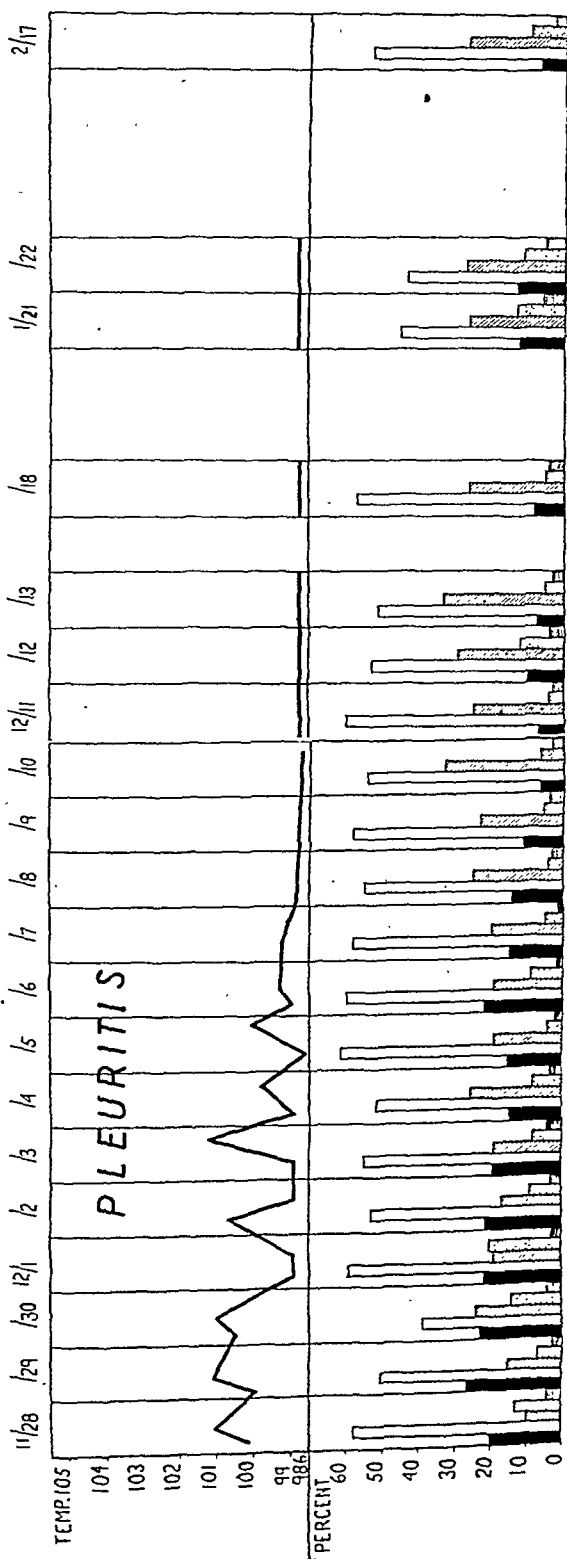


CHART IV.—Hemogram of patient V. S., who recovered from pneumonia after a complicating pleuritis.

admitted for pain in her right chest, chilliness, fever and general muscular pain for 4 days. Previous to this acute onset she had a productive cough for 2 months and complained of occasional head colds. On examination she appeared acutely ill, dyspneic and had rusty sputum. Her right side from the second to the eighth rib posteriorly was dull and the voice sounds were increased in intensity. Fine râles were scattered over this area. The blood culture was negative and the sputum showed Type II pneumococcus.

TABLE 4.—HEMOGRAM OF CASE 3; RECOVERED FROM PNEUMONIA AFTER A COMPLICATING PLEURITIS.

Date.	W.B.C.	Immature polys.		Adult polys.		Lymphocytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1930											
Nov. 28 . . .	12.7	20	2.5	57	7.2	10	1.3	12	1.5	2	.250
29 . . .	7.2	27	1.9	50	3.6	15	1.1	7	.5	1	.075
30 . . .	9.6	22	2.1	38	3.6	23	2.2	14	1.3	2	.200
Dec. 1 . . .	12.0	21	2.5	58	7.1	9	1.1	10	1.2	2	.250
2 . . .	16.0	21	3.4	52	8.3	16	2.6	8	1.3	2	.325
3 . . .	11.0	19	2.1	55	6.1	19	2.1	7	.775	2	.225
4 . . .	8.2	14	1.1	51	4.2	25	2.1	7	.575	2	.150
5 . . .	8.1	15	1.2	60	4.9	19	1.5	4	.325	1	.075
6 . . .	10.8	11	1.2	60	6.5	19	2.1	8	.85	1	.100
7 . . .	8.0	15	1.2	58	4.6	20	1.6	5	.4	1	.075
8 . . .	12.8	14	1.8	55	7.0	25	3.2	3	.375	2	.250
9 . . .	7.6	11	.85	58	4.4	22	1.7	5	.375	3	.225
10 . . .	7.8	6	.45	54	4.2	32	2.5	6	.45	2	.150
11 . . .	6.0	7	.425	60	3.6	25	1.5	4	.25	3	.175
12 . . .	5.5	10	.55	53	2.9	29	1.6	7	.4	3	.150
13 . . .	8.1	7	.575	51	4.1	33	2.7	5	.4	3	.250
18 . . .	6.7	8	.525	57	3.8	26	1.7	5	.325	4	.250
1931											
Jan. 21 . . .	5.8	12	.7	43	2.6	26	1.5	13	.75	6	.350
22 . . .	6.1	13	.8	43	2.6	27	1.6	11	.675	5	.300
Feb. 17 . . .	4.7	7	.325	53	2.5	27	1.2	10	.475	3	.150

The important features of this case are: (a) The maintenance of a fairly high immature polymorphonuclear count with the initial defervescence (December 1, 1930) suggesting a possible complication, followed by rather marked pleuritis; (b) the failure of a sustained high lymphocyte count; (c) the early appearance and persistence of eosinophils. This type of patient, who convalesces slowly, or develops a complication following the acute illness, invariably shows a tardy response of lymphocytes.

CASE 4.—P. C. represents another case in which there is a difficulty in maintaining a sustained lymphocytosis during convalescence. This patient had a left lower lobar pneumonia with Friedländer bacillus as a causative organism. Although at times he would show as many as 39 per cent lymphocytes, this was transitory and they would sink soon below 20 per cent. Not for 2 months did he show a high sustained lymphocyte count. This organism is prone to cause chronic pulmonary abscesses, and during this patient's convalescence he frequently expectorated large amounts of pus and Roentgen ray films showed suggestive shadows. It was not surprising, therefore, that 5 months after discharge he returned with an acute infection, chest pain and Friedländer bacilli were still recoverable from his sputum. Table 5 shows the blood counts.

TABLE 5.—HEMOGRAM OF CASE 4; FOLLOWING A PULMONARY FRIEDLÄNDER BACILLUS INFECTION, DEVELOPED A RELAPSE AFTER SEVERAL MONTHS.

Date.	W.B.C., total.	Immature polys.		Adult polys.		Lympho- cytes.		Monocytes.		Eosinophils.	
		Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.
1930											
Oct. 18.	20.6	20	2.5	26	5.6	20	4.1	30	12.6	4	.825
19.	13.8	14	1.9	32	4.4	25	2.1	27	3.7	2	.275
20.	23.2	21	4.9	31	5.4	29	7.0	17	3.9	2	.450
21.	22.0	24	5.3	44	9.9	20	4.4	10	2.2	2	.450
22.	18.0	13	2.3	41	7.4	32	5.8	10	1.8	3	.550
23.	22.8	8	1.8	58	13.2	22	5.0	10	2.3	2	.450
24.	24.6	8	2.0	64	16.2	22	5.4	4	1.0	2	.500
25.	13.8	8	1.1	63	8.8	20	2.8	8	1.1	1	.150
26.	15.6	9	1.4	52	8.3	29	3.5	8	1.2	2	.300
27.	11.2	6	.675	47	5.4	36	4.0	9	1.0	2	.225
28.	17.0	6	1.0	59	10.0	27	4.6	6	1.0	2	.350
29.	16.6	9	1.5	49	8.1	32	5.3	8	1.3	2	.325
30.	20.6	8	1.6	37	7.6	39	8.2	14	2.9	2	.400
31.	18.4	9	1.7	48	9.0	30	5.5	11	2.0	2	.350
Nov. 1.	10.8	7	.75	51	5.8	29	4.1	9	.975	4	.425
3.	13.0	8	1.0	51	6.8	30	3.9	8	1.0	3	.400
4.	16.0	5	.8	62	10.1	18	2.9	12	1.9	3	.475
1931											
Jan. 9.	9.8	5	.5	40	3.9	42	4.1	9	.875	4	.400
11.	8.7	7	.6	38	3.5	36	3.2	14	1.2	5	.450
Discharged											
May 18.	12.4	23	2.9	46	5.7	15	1.9	13	1.6	2	.250

CASE 5.—A man (F. R.), suffering from Type I pneumococcus, with 300 colonies per cubic centimeter of blood, recovered from his acute pulmonic condition after being given massive doses of serum and developed a post-pneumonic arthritis. Table 6 is an abbreviated account of his hemogram which was studied daily. On admission (January 20, 1931) he had a fairly low total count and had a marked "shift to the left" with a depression of lymphocytes, monocytes and eosinophils and his temperature was 104° F. For the next 5 days his condition continued precarious, with sustained fever, marked "shift to the left" and his total white blood count increased. On January 24 his culture was negative, his temperature dropped to 100° F. on January 25 and his immature polymorphonuclears decreased markedly on January 26. Although the patient felt very much better at that time, nevertheless there was no further reduction of immature polymorphonuclears and no rise in monocytes. On February 2 he complained of left sternoclavicular and shoulder-joint pain which was at first considered a serum reaction. However, this pain did not disappear and it was not until February 8 that a moderate rise in monocytes occurred. During the next few days many boils appeared, widely distributed over his body, which yielded *Staphylococcus albus*. On February 26 his lumbar joints were involved. Daily counts were performed until his discharge, and although he had an occasional lymphocyte rise (March 7 and March 15) this was only transitory and the same was true of the eosinophil response (March 16 and March 21). When he was finally discharged to a convalescent home (March 23), 2 months after admission, he still had an abnormally high immature polymorphonuclear count, a low lymphocyte count and functional and Roentgen ray evidence of a chronic inflammatory process of the left shoulder, sternoclavicular and of the lumbar vertebral joints.

The striking facts of this case are the persistence of a high immature polymorphonuclear count and the failure of the lymphocytes

to rise. The latter finding is almost diagnostic of delay in the convalescent phase.

TABLE 6.—HEMOGRAM OF CASE 5; SUFFERING FROM PNEUMONIA, DEVELOPED POLYARTHRITIS DURING RECOVERY.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Jan. 20 . .	7.4	37	55	6	2	0
21 . .	18.2	72	22	5	1	0
22 . .	15.8	76	21	2	1	0
23 . .	21.0	59	35	5	1	0
24 . .	16.2	46	48	4	2	0
25 . .	13.8	53	35	6	3	1
26 . .	12.6	30	47	13	7	0
28 . .	13.4	26	67	3	4	0
30 . .	9.8	25	56	11	6	1
Feb. 2 . .	11.0	23	61	9	5	1
8 . .	12.4	20	49	17	12	0
13 . .	9.0	21	54	18	6	1
15 . .	14.4	25	55	14	5	0
17 . .	13.4	26	60	10	4	0
19 . .	9.0	16	55	19	8	1
21 . .	9.1	14	63	19	3	1
23 . .	8.4	21	62	12	5	0
25 . .	11.1	22	47	20	8	2
26 . .	13.0	18	53	19	8	1
Mar. 6 . .	9.6	19	58	10	10	1
7 . .	13.0	13	40	31	13	2
8 . .	11.3	14	56	17	10	2
14 . .	13.3	21	49	18	9	3
15 . .	11.6	15	43	27	11	3
16 . .	15.2	24	51	14	6	4
17 . .	13.6	21	51	15	10	2
21 . .	11.3	22	48	19	6	5
22 . .	11.0	25	53	12	7	2
23 . .	11.2	20	51	18	10	1

While delay in convalescence is being considered it might be of interest to present the hemograms of 2 patients suffering from acute rheumatic fever. (Chart V and Table 7; and Table 8.) Both per cent and total values are charted in Chart V to show that no appreciable difference can be demonstrated graphically.

CASE 6.—J. O'C. was admitted suffering from joint pain of a few days' duration. He responded well to salicylates, his temperature dropped promptly and he left the hospital against advice 15 days after admission. One day after discharge his pain recurred and he entered the ward 1 week later with a distinct cardiac lesion. After a week in the hospital he left again against advice and returned 5 days later to the out-patient department with moderate pain, but refused to enter the ward.

The hemogram (Chart V, Table 7) shows that at no time did his immature polymorphonuclears fall to normal. His monocytes were high early in his illness, a characteristic of joint involvement. His lymphocytes

began to rise, suggesting beginning convalescence, but this increase was not sustained. He had an occasional eosinophil rise.

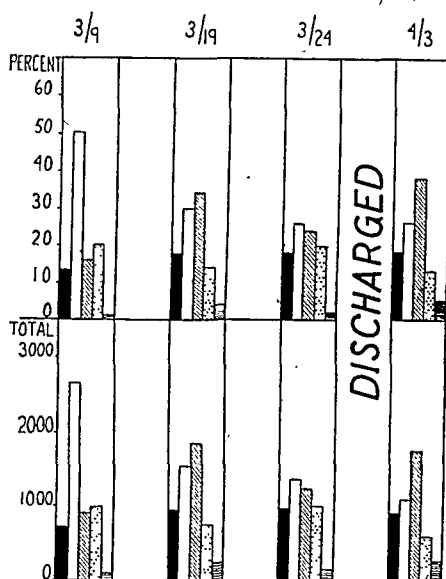


CHART V.—Hemogram of patient J. O'C., suffering from rheumatic fever, who developed a cardiac lesion.

TABLE 7.—HEMOGRAM OF CASE 6; SUFFERING FROM RHEUMATIC FEVER, DEVELOPED A CARDIAC LESION.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Mar. 9 . .	5.3	13	50	16	20	1
19 . .	5.3	18	30	34	14	4
24 . .	5.0	18	26	24	20	2
Left the hospital against advice						
Apr. 3 . .	4.6	18	26	38	13	5
10 . .	6.9	17	24	43	14	2
Left the hospital against advice						
Apr. 5 . .	10.2	10	61	24	4	0
O. P. D. .						

CASE 7.—J. D. was admitted to the ward with acute joints and insisted upon leaving 1 week after admission because he felt perfectly well. But 5 days later he returned not only with acute joints but with signs suggestive of a mitral lesion. This time he remained in bed for 6 weeks. He returned 3 weeks after discharge to the out-patient department feeling well. This patient's hemogram (Table 8) indicated no evidence of convalescence upon his first discharge from the hospital. But on his return to the out-patient department his hemogram suggested that he was in a convalescent stage as judged principally by his high lymphocyte count. It is of interest to note that in this case there was very little rise in monocytes, a marked increase of which is common in joint involvement, but a

characteristic eosinophilia was present which is typical in most rheumatic fever patients. This patient's sedimentation rate, corrected for cell volume, was 1.9 on February 28, 1931 and 0.48 on March 15. The latter rate is found in convalescents.

TABLE 8.—HEMOGRAM OF CASE 7; HAD A RELAPSE IN THE COURSE OF RHEUMATIC FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1931						
Mar. 12 . .	6.2	13	47	29	7	3
14 . .	11.5	10	70	15	4	1
16 . .	8.0	12	54	22	7	5
19 . .	10.8	16	44	29	7	4
Left the hospital against advice						
Mar. 24 . .	5.8	14	30	37	10	8
Apr. 2 . .	8.4	11	41	34	7	7
9 . .	7.0	8	45	34	6	7
16 . .	5.2	10	47	30	6	6
23 . .	8.4	19	45	25	5	6
May 5 . .	9.5	5	43	37	8	5
Discharged						
May 22 . .	7.8	8	43	42	5	3
O. P. D.						

The problem of the relationship of lymphocyte rise to convalescence is of great importance in handling patients. This is especially true in those conditions in which serious complications may ensue if a patient is considered fully recovered too quickly. In this connection it is of interest to present the following case:

TABLE 9.—HEMOGRAM OF CASE 8; SUFFERED FROM RHEUMATIC FEVER AND LEFT THE HOSPITAL WHILE STILL CONVALESCING.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 18 . .	6.7	12	58	20	9	1
19 . .	10.2	5	62	25	7	1
20 . .	7.8	8	51	22	18	1
21 . .	8.7	4	56	26	12	2
22 . .	4.5	3	51	35	9	2
23 . .	9.5	4	50	31	12	3
24 . .	6.9	3	43	46	4	4
25 . .	6.9	3	58	35	3	1
26 . .	7.6	3	44	42	8	3
27 . .	7.1	2	46	45	5	2
28 . .	7.4	4	33	50	8	5
Dec. 1 . .	6.3	4	42	44	7	3
5 . .	7.7	2	44	44	6	4

CASE 8.—A young man (C. C.), who came in suffering from acute rheumatic fever, defervesced rapidly, showed no evidence of joint involvement

in a few days and his immature polymorphonuclear count became normal 2 days after admission and 6 days after the onset of his illness. However, his lymphocyte count (Table 9) which rose promptly was still high when he was discharged. Unfortunately he did not return for further study.

It might be of interest to study some other hemograms which show characteristic features. The findings in acute tonsillitis are striking.

CASE 9.—Table 10 illustrates the blood counts in an adult female (A. W.), admitted with a temperature of 102° F. and an acutely inflamed throat. Within 48 hours her temperature dropped and her general and local condition improved. In about a week she felt normal.

TABLE 10.—HEMOGRAM OF CASE 9; SUFFERED FROM ACUTE TONSILLITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1929						
Nov. 30 . .	12.0	27	49	12	11	1
Dec. 1 . .	8.2	27	38	15	15	5
2 . .	5.9	27	25	29	12	7
3 . .	5.2	11	32	38	13	6
4 . .	7.1	13	48	24	8	7
5 . .	6.2	5	48	33	10	4
9 . .	8.9	4	39	41	12	4
12 . .	6.4	6	40	39	14	1
16 . .	5.2	4	36	46	9	5
18 . .	6.4	5	49	36	6	4

CASE 10.—Table 11 shows a hemogram of a young male (J. S.), who developed acute tonsillitis during the course of convalescence from typhoid fever. He ran a fever varying from 101° to 104.5° F. for 4 days. His hemogram starts on the third day of his acute illness.

TABLE 11.—HEMOGRAM OF CASE 10; DEVELOPED ACUTE TONSILLITIS DURING THE COURSE OF CONVALESCENCE FROM TYPHOID FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Oct. 14 . .	14.6	23	50	21	5	1
15 . .	12.4	13	39	29	13	6
16 . .	9.5	8	32	47	9	4
17 . .	10.0	9	41	34	7	9
18 . .	13.6	10	31	34	8	17
19 . .	13.0	9	39	40	6	6
20 . .	13.7	9	47	28	6	10
23 . .	15.4	6	45	37	7	5
25 . .	13.8	4	43	38	5	10
27 . .	10.6	5	43	40	4	8
29 . .	7.1	6	36	48	4	6
Nov. 1 . .	9.5	3	37	50	4	6
6 . .	14.4	3	41	39	11	6
24 . .	8.1	3	43	38	5	11

In both cases the striking feature is a high and sustained eosinophil count and the rapid attainment of a high lymphocyte count immediately upon recovery or almost as soon as the immature polymorphonuclears dropped to normal.

The next 2 cases illustrate the hemograms in 2 patients suffering from meningococcus meningitis.

CASE 11.—Table 12 shows the blood findings in a Puerto Rican girl (I. L.), aged 14 years, who was acutely ill on admission and responded rapidly to serum. The counts of November 21 and November 26 were performed during her reaction to serum.

TABLE 12.—HEMOGRAM OF CASE 11; SUFFERED FROM MENINGOCOCCUS MENINGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1928						
Nov. 6 . .	11.7	36	44	9	10	1
9 . .	10.4	31	22	30	15	1
12 . .	15.4	23	47	23	5	2
13 . .	15.1	11	60	22	3	4
14 . .	19.4	6	59	25	9	1
16 . .	11.2	6	45	37	9	3
21 . .	7.3	10	44	39	5	2
26 . .	8.2	5	33	55	2	5

CASE 12.—Table 13 gives the findings in the case of a boy, aged 12 years (R. G.), during his convalescence.

In both patients a high lymphocytic count was obtained as convalescence progressed and an increase of eosinophils.

TABLE 13.—HEMOGRAM OF CASE 12; SUFFERED FROM MENINGOCOCCUS MENINGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 11 . .	5.9	8	50	25	15	2
12 . .	3.3	7	55	27	6	5
13 . .	3.8	5	56	28	8	3
14 . .	4.6	6	51	33	6	4
15 . .	4.0	6	44	39	6	5
16 . .	6.1	7	41	40	9	3
20 . .	5.5	6	41	39	10	4

CASE 13.—Table 14 shows the results obtained in a male patient (T. N.), aged 66 years, who developed a lymphangitis of his right leg following a superficial injury. His temperature was 103° F. on admission and dropped, after local treatment, in 4 days. This hemogram shows the occurrence of a high eosinophil count early in recovery and the maintenance of a high lymphocyte count for a considerable period after his immature polymorphonuclears returned to normal.

TABLE 14.—HEMOGRAM OF CASE 13; DEVELOPED LYMPHANGITIS.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Oct. 9 . .	6.9	33	34	12	19	2
10 . .	11.0	28	48	7	15	2
11 . .	10.0	15	57	12	11	5
12 . .	9.3	16	24	27	27	6
13 . .	8.2	17	34	23	19	7
14 . .	6.5	11	52	26	7	4
15 . .	9.3	9	36	44	8	3
16 . .	9.1	5	28	52	12	3
17 . .	8.9	3	43	36	14	4
18 . .	14.9	5	43	42	9	1
19 . .	8.0	5	26	57	9	3
20 . .	11.5	4	41	49	5	1
21 . .	9.1	7	39	48	5	1
22 . .	8.6	4	47	43	4	2
24 . .	10.6	7	42	48	2	1

TABLE 15.—HEMOGRAM OF CASE 14; SUFFERED FROM SCARLET FEVER.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1929						
Nov. 22 . .	8.3	28	60	5	4	4
23 . .	8.2	30	50	8	8	4
24 . .	10.6	37	41	10	7	5
25 . .	15.7	32	47	6	10	5
26 . .	15.5	19	51	15	13	2
27 . .	15.0	17	52	13	16	2
28 . .	17.0	13	58	14	12	3
29 . .	14.0	17	49	16	16	2
30 . .	11.8	11	57	16	13	3
Dec. 1 . .	18.1	10	72	10	5	3
2 . .	12.8	10	61	10	15	4
3 . .	15.3	7	66	16	9	2
4 . .	12.0	6	67	16	7	4
5 . .	9.6	6	45	26	14	9
6 . .	11.5	5	61	18	11	5
7 . .	14.9	5	66	14	14	1
8 . .	13.0	3	63	17	12	5
9 . .	10.9	3	65	18	7	7
10 . .	8.5	1	52	29	10	8
11 . .	9.1	4	49	27	11	9

CASE 14.—Table 15 illustrates the findings in a female patient (G. P.), suffering from scarlet fever. The interesting features of this hemogram are the prolonged absence of an adequate lymphocyte response and the maintenance of a high eosinophil count. This patient entered the hospital with a temperature of 104° F. In 8 days it dropped to normal. Two days later she received news that her child died and she had a severe emotional reaction. Although her temperature rose to 103° F., her hemogram

showed no change. In the opinion of Professor Schilling her hemogram represented a typical illustration of recovery from the acute illness, but the failure of a marked lymphocytic rise to occur indicated a delay in convalescence.

The next 2 cases illustrate the effect of minor complications on the hemogram during the course of convalescence.

CASE 15.—Table 16 represents the blood counts in a patient (H. P.), suffering from acute lobar pneumonia during the course of his recovery. This was uneventful and he showed a typical recovery hemogram with a return of his immature polymorphonuclears to normal ("shift to the right") and rise of his lymphocytes. On February 18, 1931, he returned to the follow-up clinic complaining of an upper respiratory infection and a pain in his chest. The latter was found to be due to a slight pleuritis. It is of interest to note that his immature polymorphonuclears showed a distinct increase and that his lymphocytes and monocytes were markedly depressed.

TABLE 16.—HEMOGRAM OF CASE 15; DEVELOPED A PLEURITIS 3 MONTHS AFTER RECOVERY FROM AN ATTACK OF LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Nov. 18 . .	11.4	14	71	11	3	1
19 . .	8.1	12	71	8	8	1
20 . .	12.8	7	75	12	5	1
21 . .	16.9	9	56	26	8	1
22 . .	6.2	5	57	25	12	1
23 . .	8.8	4	66	17	11	2
24 . .	5.8	3	71	19	5	2
25 . .	8.7	10	70	13	5	2
26 . .	5.5	5	41	34	16	4
27 . .	6.5	4	48	40	5	3
28 . .	4.3	2	49	34	10	5
Dec. 9 . .	7.6	6	46	39	8	1
1931						
Feb. 18 . .	13.0	12	70	15	0	2

CASE 16.—Table 17 illustrates a similar condition. This patient was a young man (G. S.), suffering from Type I pneumonia from which he made a rapid and uneventful recovery except for an attack of serum sickness. He returned regularly for examination after his discharge. On February 18, 1931, his count showed a slight "shift to the left," although his lymphocytes remained high. Two days after this visit he developed a severe tonsillitis. This finding is in keeping with the fact that the blood count will change as long as 48 hours before the patient shows symptoms or signs of an acute infection. This rapid response of the blood cells is also seen in this case during his serum sickness. On December 14, 1930, a count was performed showing a sudden depression of his total count and a marked increase of his eosinophils. The blood was obtained for examination at 10 A.M. Not until 5 P.M., 7 hours later, did he develop urticaria and joint pain. When last seen this patient was in perfect condition and had a normal hemogram, including a normal lymphocyte count.

TABLE 17.—HEMOGRAM OF CASE 16; DEVELOPED AN ACUTE UPPER RESPIRATORY INFECTION AFTER CONVALESCENCE FROM LOBAR PNEUMONIA.

Date.	W.B.C.	Immature polys, per cent.	Adult polys, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Eosinophils, per cent.
1930						
Dec. 12 . .	6.0	24	49	14	10	3
13 . .	7.8	16	59	12	11	2
14 . .	4.7	11	63	12	9	5
15 . .	8.4	17	59	14	8	2
16 . .	6.0	9	45	27	17	2
17 . .	10.8	7	41	38	13	1
18 . .	4.7	8	41	40	10	1
21 . .	7.8	7	47	35	7	4
24 . .	7.6	5	57	28	8	2
25 . .	5.8	7	51	33	7	2
29 . .	6.0	6	52	32	6	4
1931						
Jan. 13 . .	8.4	5	50	35	6	4
28 . .	6.2	6	44	38	11	1
Feb. 18 . .	4.6	10	41	36	12	1
Mar. 25 . .	7.0	4	61	28	5	2

Discussion. In a recent Harvey address Gay⁶ has emphasized the importance of the cellular reaction of the body to infection and pointed out that in the response of the blood and tissue cells we have our most delicate indication of the defense mechanisms. Schilling⁷ has extended this view to convalescence. His hemogram gives us an excellent indication of the three phases in recovery from an infection—subsidence of the acute stage, convalescence, complete recovery.

This principle has been used extensively in the study of tuberculosis. This disease lends itself especially well for such research because patients have been educated to take a long convalescence from the tuberculous infection. Cunningham and Tompkins⁸ and Durel⁹ pointed out the importance of a low monocyte-lymphocyte ratio for favorable prognosis. Bredick¹⁰ applied the details of the Schilling hemogram to tuberculosis, and concluded that this was the best single guide of the progress of the disease. Dunlop¹¹ came to the same conclusion. Brock¹² and Guggenheim¹³ pointed out that the acute septic state of tuberculosis shows the same blood picture as any other acute infection and that only as localization and recovery occur does the hemogram give special details of the progress of the patient. It should be emphasized, however, that tuberculosis shows no different hemogram even in convalescence than any other infection. Only the duration of the various phases differs. An important practical use of the hemogram was made by Griesbach.¹⁴ He applied this to pneumothorax therapy and found

that the air might be removed with complete recovery after the lymphocytes return to normal. Doan and Sabin¹⁵ have studied the relation of cell response in tuberculosis by using the chemical derivatives from the organism and have thrown much light on the mechanisms involved.

Stuppy, Cannon and Falk¹⁶ report an interesting experiment showing, they believe, that the cellular response is allergic in nature. In their work they found that experimental pneumonia produced in rabbits caused the appearance mostly of polymorphonuclear cells in the lungs. If the rabbits were immunized first with vaccine the histologic picture presented mostly histiocytes and some eosinophils. This illustrates strikingly the variation of cellular response to the same infection with variation in resistance.

The relation of the various types of cells to each other is of great interest and importance. It is obvious that one type of cell can have a depressing influence on other types.¹⁷ This is seen in the relatively as well as absolutely low lymphocyte and monocyte counts when there is a predominance of immature polymorphonuclears. Eosinophils are usually considered as evidence of some allergic effect.¹⁸ Certainly it is true that in most conditions in which a distinct allergic response is seen one finds the highest and most sustained eosinophil count, *e. g.*, scarlet fever,¹⁹ acute tonsillitis and erysipelas. Incidentally these conditions are all caused by some form of hemolytic streptococcus. In some cases of rheumatic fever eosinophilia is prominent during convalescence.^{20,21} The importance of eosinophilia depends upon the relation of complications to an allergic state.^{22,23}

The most important practical consideration in studying the hemogram is to remember that it is only one nonspecific laboratory factor and to be of any help in a general clinical consideration it is necessary to make sequential counts at frequent intervals rather than isolated determinations. What a patient shows at a particular moment is only of importance in so far as it throws light on the direction a patient is going.

Conclusions. 1. In recovery from an acute infectious disease three more or less distinct phases may be demarcated by the hemogram: subsidence of the acute stage, convalescence, complete return to normal.

2. The subsidence of the acute stage is characterized by a decrease in immature polymorphonuclears and a marked, even if transitory, rise in monocytes.

3. Convalescence is characterized by a normal immature polymorphonuclear count, a marked rise in lymphocytes (often above 40 per cent) and a variable eosinophilia.

4. Complete recovery is characterized by a return of the lymphocytes to a normal range.

BIBLIOGRAPHY.

1. Schilling, V.: *The Blood Picture*, 7th and 8th ed., St. Louis, The C. V. Mosby Company, 1929, p. 239.
2. Reznikoff, P.: *Immature White Blood Counts in Infectious Diseases*, J. Am. Med. Assn., 1920, 93, 963.
3. Swift, H. F.: *Acute Rheumatic Fever*, Oxford Medicine, New York, Oxford University Press, 1927, 5, 11.
4. Garrey, W. E., and Butler, V.: *Physiological Leucocytosis*, Am. J. Physiol., 1929, 90, 355.
5. Medlar, E. M.: *The Extent of the Variations in Leukocytes of Normal Individuals*, Am. J. Med. Sci., 1929, 177, 72.
6. Gay, F. P.: *Harvey Lecture*, Baltimore, The Williams & Wilkins Company, 1931 (in press).
7. Schilling, V.: *Das Hämogramm in der Poliklinik*, Ztschr. f. klin. Med., 1924, 99, 232.
8. Cunningham, R. S., and Tompkins, E. H.: *The White Blood Cells in Human Tuberculosis*, Am. Rev. Tuberc., 1928, 17, 204.
9. Durel, W. J.: *The Clinical Value of the Neutrophil Nucleus Index, the Lymphocyte Index and Monocyte Index in Tuberculosis*, New Orleans Med. and Surg. J., 1929, 81, 480.
10. Bredick, J. F.: *The Schilling Blood Differential Count in Tuberculosis*, Am. Rev. Tuberc., 1929, 20, 52.
11. Dunlop, D. M.: *The Leucocytic Reaction to Tuberculosis: Its Value in Prognosis*, Edinburgh Med. J., 1930, 37, 174.
12. Brock, B. L.: *The Role of the Leucocytes in Tuberculosis*, Am. Rev. Tuberc., 1930, 21, 745.
13. Guggenheim, M.: *Die Linksverschiebung im weissen Blutbild bei der Tuberkulose*, Beitr. z. Klin. d. Tuberk., 1930, 73, 625.
14. Griesbach, R.: *Das differenzierte weisse Blutbild bei der Kallapstherapie der Lungentuberkulose*, Ztschr. f. Tuberk., 1930, 56, 177.
15. Doan, C. A., and Sabin, F. R.: *The Relation of the Tubercle and the Monocyte-Lymphocyte Ratio to Resistance and Susceptibility in Tuberculosis*, J. Exp. Med., 1930, 52, 113.
16. Stuppy, G. W., Cannon, P. R., and Falk, I. S.: *Nature of Local Immunity in Lungs of Rabbits Immunized Against Pneumococci*, Proc. Soc. Exp. Biol. and Med., 1929, 26, 214.
17. Camp, W. J. R.: *The Effect of Drugs on the Number of Circulating White Blood Cells*, J. Lab. and Clin. Med., 1927, 31, 206.
18. Schilling, V.: *The Blood Picture*, 7th and 8th ed., St. Louis, The C. V. Mosby Company, 1929, p. 261.
19. Silberstein, M. S.: *Schilling's Leukocyte Picture in Scarlet Fever*, *Pediatra*, Moscow, 1928, 12, 227; abstracted by J. Am. Med. Assn., 1928, 91, 1846.
20. Perry, C. B.: *The Leukocyte Count in Rheumatic Heart Disease in Childhood*, Arch. Dis. Child., 1929, 4, 247.
21. Piccoli, G.: *Cytologic Observations on Blood in Acute Articular Rheumatism*, Gior. di clin. med., 1930, 11, 981; abstracted by J. Am. Med. Assn., 1931, 96, 306.
22. Zinsser, H., and Takeo, T.: *An Experimental Analysis of Bacterial Allergy*, J. Exp. Med., 1926, 44, 753.
23. Derick, C. L., Hitchcock, C. H., and Swift, H. F.: *Reactions of Rabbits to Non-hemolytic Streptococci: III. A Study of Modes of Sensitization*, J. Exp. Med. 1930, 52, 1.

ACHLORHYDRIA WITH A REVIEW OF 210 CASES IN PATIENTS WITH GASTROINTESTINAL COMPLAINTS.*

By H. L. BOCKUS, M.D.,

PROFESSOR OF GASTROENTEROLOGY,

J. BANK, M.D.,

ASSOCIATE IN GASTROENTEROLOGY,

AND

J. H. WILLARD, M.D.,

ASSISTANT IN GASTROENTEROLOGY.

PHILADELPHIA, PA.

(From the Gastrointestinal Services, Graduate Hospital of the University of Pennsylvania and Presbyterian Hospital.)

FOLLOWING the introduction of the fractional method of gastric analysis by Rehfuß,¹ it soon became obvious that a diagnosis of achylia gastrica based upon a single extraction of stomach contents was often erroneous. Eggleston² in a large series of cases compared the Rehfuß method with the older single extraction Ewald test and noted the incidence of achlorhydria to be twice as great by the latter method. Later it was found that a single fractional analysis is not infallible in the diagnosis of achlorhydria, since repeated examinations with the same or different test meals often gave a variable secretory response. The use of histamin as a gastric stimulant by Popielski³ in 1920 and Carnot, Koskawski and Liebert⁴ in 1922 made it possible to measure accurately the function of the stomach glands. In 1925 Gompertz and Voorhaus⁵ applied the subcutaneous injection of histamin for the purpose of differentiating true from so-called false achylia. In a comparative study between the ordinary fractional analysis and a fractional analysis following the injection of histamin, two of us⁶ have shown that only 53 per cent of stomachs in which achlorhydria was diagnosed after the Rehfuß test failed to secrete gastric juice after histamin injection. The increased accuracy thus available has shown that achylia gastrica is a comparatively rare condition and has made it possible to clarify the existing state of confusion in describing deficiency in gastric secretion.

This report comprises a review of 210 cases of achlorhydria occurring in patients with gastrointestinal complaints. The cases were selected promiscuously from our service in two large city hospitals and from private practice. The diagnosis of achlorhydria was based upon finding no free hydrochloric acid by fractional gastric analysis. In each instance the fasting gastric residuum was extracted and a meal consisting of 2 slices of ordinary white

* Read before the Pan-American Medical Association in Mexico City, July 29, 1931.

bread (35 grams) and 350 cc. of water was given. Extractions were removed every fifteen minutes for two hours unless the stomach emptied its contents into the duodenum previously. All patients upon whom gastric surgery had been performed were excluded.

Sex and Age Incidence of Achlorhydria in Health and Disease. Strangely enough, there is a paucity of literature on the probable expectancy of this condition. In much of the older literature the diagnosis was based upon a single extraction of the stomach contents. The aggregate of existing reports indicates a gradually increased incidence of achlorhydria with age. Wright recovered acid from all but 4 of 250 children between the ages of 6 and 15 years. Bennett and Ryle⁸ found achlorhydria in 10 per cent of healthy students. Its frequency is variously given after the age of

Per cent of cases

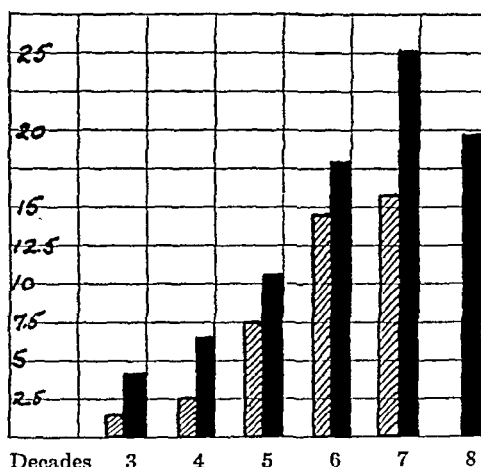


CHART I.—Showing incidence of achlorhydria in the various decades.
Our series ▨ Compared with Vanzant's ■

50 years as 20 to 50 per cent. Vanzant⁹ recently reviewed 3381 gastric analyses performed on patients with normal digestive tracts and the absence of any other condition which is ordinarily considered to modify gastric acidity. The incidence of achlorhydria increased from 4 per cent at the age of 20 years to approximately 26 per cent at the age of 60 years. Women were more subject to achlorhydria than men regardless of age. A decrease in its incidence was found after the age of 70 years. Sixty-one cases in our series were selected from the office files of one of us by going over a series of 1075 consecutive gastric analyses in which all of the data were available. Table 1 and Chart I compare this series of 61 cases with that of Vanzant. The incidence of achlorhydria in our series (5.7 per cent) is much lower than in Vanzant's (12.1 per cent). Her analyses were terminated in 105 minutes whereas ours were continued 2 hours unless the stomach became empty before the 2-hour

extraction. We excluded about 10 cases because of the presence of free acid in the 2-hour extraction. The tendency to increase with age was present in both series. The occurrence of achlorhydria increased gradually with advancing years up to the age of 70 years. Our incidence in the male sex was 4.8 per cent and in the female 6.6 per cent, compared with Vanzant's incidence of 10.8 per cent in the male and 13.8 per cent in the female sex.

TABLE 1.—SEX AND AGE INCIDENCE OF ACHLORHYDRIA IN 61 CASES (1075 CONSECUTIVE GASTRIC ANALYSES).

<i>Male.</i>						
Age decades.	This series.			Vanzant's series.		
	Cases achlor-hy-dria.	Total cases.	Per cent achlor-hy-dria.	Cases achlor-hy-dria.	Total cases.	Per cent achlor-hy-dria.
0 to 9	0	1	0	0	0	0
10 to 19	0	10	0	0	0	0
20 to 29	1	118	0.85	8	331	2.4
30 to 39	5	169	3.0	14	401	3.5
40 to 49	7	122	5.7	46	466	9.9
50 to 59	9	83	10.8	64	352	18.2
60 to 69	4	39	10.3	60	259	23.1
70 to 79	0	5	0	9	45	20.0
Total	26	547	4.8	201	1854	10.8
<i>Female.</i>						
0 to 9	0	0	0	0	0	
10 to 19	0	10	0	0	0	
20 to 29	2	115	1.7	12	250	4.8
30 to 39	4	186	2.1	37	389	9.5
40 to 49	10	113	8.8	35	278	13.0
50 to 59	13	75	17.3	58	320	18.0
60 to 69	6	26	23.0	54	196	27.6
70 to 79	0	3	0	6	31	19.4
Total	35	528	6.6	202	1464	13.8
<i>Total Cases.</i>						
0 to 9	0	1	0	0	0	0
10 to 19	0	20	0	0	0	0
20 to 29	3	233	1.3	20	581	3.4
30 to 39	9	355	2.5	51	790	6.5
40 to 49	17	235	7.2	81	744	10.9
50 to 59	22	158	14.0	122	672	18.1
60 to 69	10	65	15.4	114	455	25.0
70 to 79	0	8	0	15	76	19.7
Total	61	1075	5.7	403	3318	12.1

Paradoxical as it may appear, one might conclude from this comparison that patients consulting a physician because of gastrointestinal complaints show a lower incidence of achlorhydria than a similar group of normal patients of like age and sex. One explanation may be that diseases giving rise to hyperacidity are a more common cause of gastrointestinal complaints than those producing anacidity. So-called hyperacidity is more often associated with disturbances of motility, a factor of greater importance in the production of symptoms than secretory deficiencies.

Per cent of cases

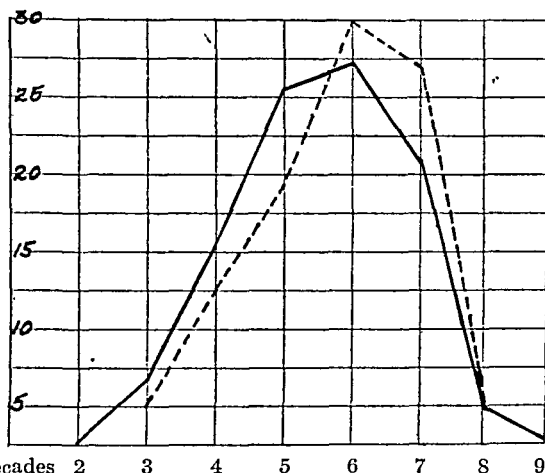


CHART II.—Comparison of age distribution of this series of 210 cases of achlorhydria with Vanzant's series of 403 cases in normals.
This series ——— Vanzant's - - - - -

TABLE 2.—AGE COMPARISON OF 210 CASES OF ACHLORHYDRIA IN OUR PATIENTS WITH 403 CASES OF ACHLORHYDRIA IN NORMAL INDIVIDUALS (VANZANT'S).

Decade.	Achlorhydria in our patients.		Achlorhydria normal people (Vanzant).	
	Number.	Per cent.	Number.	Per cent.
0 to 9	0	0	0	0
10 to 19	1	0.5	0	0
20 to 29	15	7.1	20	5.0
30 to 39	32	15.2	51	12.7
40 to 49	53	25.2	81	20.1
50 to 59	57	27.2	122	30.0
60 to 69	43	20.5	114	28.4
70 to 79	7	3.3	15	3.8
80 to 89	2	1.0	0	
Total	210		403	

Age Incidence of Cases With Achlorhydria. In our entire series of 210 cases of achlorhydria, 100 cases occurred in the male sex and 110 in the female sex. The age decades in which these cases occurred can be compared with a series of 403 cases reported by Vanzant (Table 2). The highest decade incidence in each series was the

sixth. Seventy-three per cent of our series and 78.5 per cent of Vanzant's occurred between 40 and 70 years. However, 48 per cent of our cases and only 37.5 per cent of Vanzant's were under 50 years of age. (See Chart II.)

The available literature based upon a study of the whole period of gastric digestion, shows a very low incidence of achlorhydria in childhood and a gradually increasing frequency up to the age of 60 years. One infers that the condition usually develops during later life and is rarely congenital and this is supported by the work of Conner.¹⁰ He found a greater frequency of achlorhydria among blood relatives of patients with pernicious anemia than among other people. His feeling that the achlorhydria was not in itself inherited was based upon finding only 15.7 per cent of achlorhydria in blood relatives under 40 years of age and 42.3 per cent in blood relatives after the age of 40 years. He concluded that the members of pernicious anemia families may inherit a tendency toward the development of achlorhydria later in life. If it were true that achylia gastrica is more apt to be congenital or hereditary, as some believe, one would expect to find a greater number of cases of true achylia in the earlier decades. We noted no essential difference between the age incidence of our cases of true achylia and of achlorhydria or pseudo-achylia.

Ordinary Fractional Gastric Analysis Compared with Histamin Gastric Analysis. The histamin test as described by two of us⁶ was used in 64 cases in which the ordinary fractional gastric analysis had previously been carried out. From 0.25 to 1 mg. of histamin was injected simultaneously with the ingestion of the test meal. A physiologic response consisting of a diffuse erythema was considered essential. This is mentioned because Gaither¹¹ has recently reported finding an achlorhydria after histamin in several cases in which an acid response was obtained by test meals without histamin. We have never failed to get an acid response to histamin in every case in which acid was present by ordinary gastric analysis. It is our feeling that experience of the type reported by Gaither may result from the use of a preparation of histamin which has lost its potency or from the use of an insufficient dose. Such errors may be prevented by discarding all tests in which histamin does not provoke a general erythema. We used primarily from 0.25 to 0.5 mg. of histamin. If no reaction was observed, a second injection was given so that the total dose amounted to 1 mg. of histamin. A failure to obtain free acid and enzymes after histamin injection warrants a definite diagnosis of achylia gastrica and such a diagnosis is never justifiable without histamin.

An apparent achylia was indicated by the absence of both free acid and gastric rennet after ordinary gastric analysis in 58 of 64 cases in which histamin was subsequently used (Table 3). Of these (15 were cases of pernicious anemia) 35 failed to respond to

TABLE 3.—ORDINARY FRACTIONAL GASTRIC ANALYSIS COMPARED WITH FRACTIONAL ANALYSIS AFTER HISTAMIN.

Case No.	Age.	Sex.	Diagnosis.	Ordinary gastric analysis.			Secretory diagnosis based upon ordinary gastric analysis.	Histamin gastric analysis.			Secretory diagnosis after histamin.
				HCl.	Total acid.	Ren-net.		HCl.	Total acid.	Ren-net.	
1	60	M.	Intestinal stasis	0	15	0	Apparent achylia	0	20	0	Achylia
4	36	F.	Intestinal stasis	0	10	0	"	0	10	0	"
1	36	F.	Intestinal stasis	0	10	0	"	0	10	0	"
7	44	M.	Spastic colitis	0	15	0	"	0	15	0	"
16	51	F.	Gastrogenous diarrhea	0	15	0	"	0	15	0	"
17	27	M.	Cardiospasm	0	15	0	"	0	20	0	"
18	56	M.	Secondary anemia	0	10	0	"	0	10	0	"
22	39	F.	Pernicious anemia	0	20	0	"	0	30	0	"
28	59	F.	Diabetes	0	10	0	"	0	10	0	"
29	67	M.	Posterolateral sclerosis	0	10	0	"	0	10	0	"
35	62	M.	Pernicious anemia	0	20	0	"	0	15	0	"
45	50	F.	Secondary anemia	0	15	0	"	0	15	0	"
46	45	M.	Pernicious anemia	0	10	0	"	0	10	0	"
54	40	F.	Spastic colitis	0	20	0	"	0	15	0	"
62	42	M.	Pernicious anemia	0	15	0	"	0	10	0	"
64	45	M.	Gastrogenous diarrhea	0	10	0	"	0	10	0	"
70	68	M.	Alcoholic gastritis	0	15	0	"	0	10	0	"
71	41	F.	Intestinal stasis	0	10	0	"	0	20	0	"
75	50	F.	Hypertension	0	25	0	"	0	20	0	"
76	46	F.	Pernicious anemia	0	30	0	"	0	15	0	"
77	55	F.	Intestinal stasis	0	10	0	"	0	10	0	"
78	59	M.	Cardiac decompensation	0	25	0	"	0	10	0	"
86	44	M.	Intestinal stasis	0	10	0	"	0	10	0	"
90	28	M.	Psychoneurosis	0	10	0	"	0	10	0	"
91	64	F.	Pernicious anemia	0	10	0	"	0	10	0	"
92	65	F.	Gastrogenous diarrhea	0	10	0	"	0	10	0	"
102	62	F.	Cholecystitis	0	15	0	"	0	10	0	"
L 4	59	M.	Gastric lues	0	15	0	"	0	15	0	"
L 11	31	F.	Gastric lues	0	20	0	"	0	15	0	"
L 13	60	M.	Lues	0	20	0	"	0	25	0	"
L 15	51	F.	Lues	0	10	0	"	0	20	0	"
W 88	52	M.	Pernicious anemia	0	20	0	"	0	20	0	"
W 89	52	F.	Pernicious anemia	0	20	0	"	0	15	0	"
W 97	21	F.	Arthritis	0	25	0	"	0	15	0	"
W 100	45	F.	Duodenal ileus	0	10	0	"	0	10	0	"
W 102	46	F.	Pernicious anemia	0	30	0	"	0	30	+	Achlorhydia
61	52	M.	Secondary anemia	0	15	0	"	0	60	+	Hypochlorhydia
20	60	F.	Biliary cirrhosis	0	15	0	"	20	60	+	Achlorhydia
21	65	F.	Gastrogenous diarrhea	0	20	0	"	0	30	+	"
31	64	M.	Portal cirrhosis	0	15	0	"	0	25	+	"
39	34	F.	Hyperthyroidism	0	15	0	"	0	30	+	"
44	60	M.	Hypertension	0	20	0	"	0	20	+	"
47	25	F.	Gastritis	0	20	0	"	0	20	+	"
68	43	F.	Melena	0	10	0	"	0	10	+	"
80	39	M.	Gastritis	0	40	0	"	40	55	+	Normal acid
87	35	M.	Spastic colitis	0	20	0	"	5	25	+	Hypochlorhydia
89	55	M.	Arteriosclerosis	0	10	0	"	0	10	+	Achlorhydia
94	56	M.	Spastic colitis	0	20	0	"	0	20	+	"
97	76	M.	Gastritis	0	20	0	"	0	30	+	"
99	39	M.	Spastic colitis	0	15	0	"	0	10	+	"
101	33	F.	Splanchnoptosis	0	10	0	"	0	30	+	"
L 1	48	F.	Gastric lues	0	10	0	"	20	40	+	Hypochlorhydia
L 14	81	F.	Lues	0	15	0	"	0	20	+	Achlorhydia
L 16	42	M.	Lues gastric ulcer	0	25	0	"	0	25	+	"
W 83	48	M.	Secondary anemia	0	20	0	"	5	15	+	Hypochlorhydia
W 94	30	M.	Intestinal stasis	0	15	0	"	0	20	+	Achlorhydia
W 103	55	F.	Splanchnoptosis	0	15	0	"	0	15	+	"
9	33	M.	Intestinal stasis	0	15	0	"	0	25	+	"
L 8	42	F.	Gastric lues	0	10	0	"	35	60	+	Normal acid
L 3	21	M.	Gastric lues	0	20	+	Apparent achlorhydia	55	70	+	Hyperacidity
33	40	F.	Spastic colitis	0	20	+	"	0	25	+	Achlorhydia
42	60	M.	Gastric hemorrhage	0	40	+	"	10	50	+	Hypochlorhydia
49	43	F.	Auricular fibrillation	0	25	+	"	5	25	+	"
L 2	27	F.	Lues	0	15	+	Apparent achlorhydia	15	40	+	"
8	34	F.	Spastic colitis	0	20	+	"	0	15	+	Achlorhydia

The acidity figures recorded represent the highest values obtained throughout the two hour test.

histamin either by acid or enzyme secretion, giving true achylia in 60 per cent of cases in which an apparent achylia was found after ordinary fractional gastric analysis. Twenty-three cases (40 per cent) showed a secretory response to histamin. Gastric rennet without hydrochloric acid appeared in 17 cases (true achlorhydria). In 4 cases an hypochlorhydria and in 2 a normal acidity resulted from histamin injection. In 6 cases an apparent achlorhydria (enzymes present) was present without histamin. Histamin failed to cause acid response in 2, but in 3 cases a hypochlorhydria, and in 1 a hyperacidity followed the injection. Experience with histamin suggests a gradual rather than sudden development of achylia. The secretion of gastric enzymes apparently persists in many stomachs after acid secretion has stopped. Hydrochloric acid is never secreted in the absence of gastric enzymes. Histamin is capable frequently of producing acid response in many instances in which only enzymes are secreted after the ordinary meal or of causing only an enzyme secretion when both acid and enzymes are absent after the ordinary test meal. The state of gastric secretion as determined by histamin injection is rarely ever improved by treatment.

Although we cannot demonstrate that gastritis is the usual cause of true achylia, the evidence at hand suggests some cause acting over a long period of time. We have never observed the sudden appearance of achylia in a patient with normal gastric secretion a short time previously; but we have followed patients with a normal acidity through the stages of hypochlorhydria until an achlorhydria developed.

TABLE 4.—COMPARISON BETWEEN TWO ORDINARY FRACTIONAL GASTRIC ANALYSES (19 CASES).

Case No.	Age.	Sex.	Diagnosis.	First analysis.			Secretory diagnosis first analysis.	Second analysis.			Secretory diagnosis second analysis.
				HCl.	Total acid.	Rennet.		HCl.	Total acid.	Rennet.	
52	51	F.	Spastic colitis	0	20	0	Apparent achylia	0	25	+	Apparent achlorhydria
L 6	55	M.	Gastric lues	0	10	0	"	20	30	+	Hypochlorhydria
W 16	49	F.	Cholecystitis	0	5	0	"	0	5	0	Apparent achylia
W 69	25	F.	Pulmonary tuberculosis	0	20	0	"	15	25	+	Hypochlorhydria
3	60	F.	Cholecystitis	0	25	+	Apparent achlorhydria	0	25	+	Apparent achlorhydria
11	31	F.	"	0	15	+	"	0	20	+	"
50	43	M.	Intestinal stasis	0	15	+	"	0	20	+	"
53	48	M.	Spastic colitis	0	25	+	"	0	25	+	"
63	41	M.	Cholelithiasis	0	30	+	"	0	25	+	"
66	27	F.	Cholecystitis	0	5	+	"	0	30	+	"
69	74	M.	Benign hour-glass	0	20	+	"	45	55	+	Normal acid
L 10	46	F.	Gastric lues	0	20	+	"	0	25	+	Apparent achlorhydria
99	58	M.	Carcinoma	0	25	+	"	15	40	+	Hypochlorhydria
W 2	30	F.	Splanchnoptosis	0	20	+	"	0	20	+	Apparent achlorhydria
W 18	51	M.	Intestinal stasis	0	15	+	"	0	20	+	"
W 23	37	F.	Intestinal stasis	0	15	+	"	15	30	+	Hypochlorhydria
W 50	56	F.	Cholecystitis	0	10	+	"	0	5	+	Apparent achlorhydria
W 52	47	F.	Cholelithiasis	0	20	+	"	0	15	+	"
W 70	62	M.	Carcinoma	0	15	+	"	45	70	+	Normal acid

The figures for acid values are the highest found during the analysis.

Recent publications by Gilman and Cowgill¹² and Vineberg and Babkin¹³ indicate that in dogs with Pavlov or Heidenhain type pouches histamin acts exclusively on the acid secreting glands, and that following an initial rise in pepsin content, probably due to flushing of the glands, there is a decrease in pepsin concentration. Our experience in these cases, using the rather crude rennet test for gastric enzymes, suggests that in many cases of achlorhydria histamin does stimulate the enzyme secreting cells.

In 19 cases the ordinary fractional gastric analysis was repeated at least once without the use of histamin. The results of this study are tabulated in Table 4. In 7 of the 19 cases (37 per cent) the degree of secretory function was later found to be greater without resorting to histamin. This clearly emphasizes the fallacy of basing a diagnosis of achylia upon one fractional gastric analysis without using histamin.

TABLE 5.—INCIDENCE OF VARIOUS DISEASES AND SYMPTOMS OCCURRING IN 210 CASES OF ACHLORHYDRIA.

Diagnosis.	Male		Female		Total.
	Achylia.	Achlor-hydria.	Achylia.	Achlor-hydria.	
1. Pernicious anemia	6	0	9	0	15
2. Anemia (not primary)	3	8	4	14	27
3. Combined lateral sclerosis	2	2	1	0	5
4. Gastritis	2	26	3	10	41
4b. Duodenitis	3	27	4	19	53
5. Gastric lues	1	3	2	3	9
6. Tertiary lues	1	10	0	2	13
7. Cancer, stomach	0	9	0	7	16
8. Cancer, elsewhere	0	1	0	2	3
9. Cholecystitis	0	3	1	12	16
10. Cholelithiasis	0	3	0	4	7
10. Visceroptosis	0	2	3	18	23
11. Spastic colitis	3	11	1	7	22
12. Mucous colitis	1	3	0	3	7
13. Ulcerative colitis	0	2	0	0	2
14. Arteriosclerosis	1	7	1	1	10
15. Hypertension	0	6	1	3	10
16. Nephritis	0	3	0	1	4
17. Cardiac disease	1	3	1	6	11
18. Arthritis	0	3	2	3	8
19. Acne rosacea	0	1	0	0	1
20. Other dermatoses	0	0	0	3	3
21. Portal cirrhosis	0	3	0	0	3
22. Banti disease	0	0	0	1	1
23. Diabetes	0	0	1	4	5
24. Pulmonary tuberculosis	0	3	0	1	4
25. Constipation (not listed under spastic colitis)	7	23	3	31	64
26. Gastrogenous diarrhea	1	8	1	11	21
27. Duodenal stasis	0	1	2	4	7
28. Cardiospasm	1	0	0	3	4
29. Giardiasis	0	0	0	1	1
30. Goiter	0	0	0	2	2
31. Psychoneurosis	1	3	0	1	5
32. Gastric ulcer	0	1	0	0	1

Significance and Incidence of Various Diseases and Symptoms in 210 Patients with Achlorhydria. A complete list of the more important diagnoses made and of the conditions which are commonly thought to be associated with achlorhydria and achylia will be seen on Table 5.

Primary Pernicious Anemia. As early as 1886 Cahn and von Mehring¹⁴ reported the absence of hydrochloric acid in a case of pernicious anemia. A true achylia gastrica (after histamin) is now generally considered to be a necessary accompaniment of this disease, although a few reports appear in the literature in which free acid or enzymes were recovered from the stomach. (Levine and Ladd¹⁵ and Grinker¹⁶). The accuracy of the diagnosis in these cases is doubtful. Many observers (Faber,¹⁷ Hurst¹⁸ and Sturtevant¹⁹) have noted the existence of achlorhydria years previous to the onset of pernicious anemia. The cure of the anemia on liver therapy is not associated with a return of gastric acidity, according to most writers. Hurst, however, mentioned 3 cases in which acid reappeared after treatment. McPeak and Neighbors²⁰ had a case of pernicious anemia in which achylia was known to have been present for 4 years, yet acid was found in the stomach 4 months after liver therapy was started. Cases of this sort are undoubtedly very rare. Johansen,²¹ Minot and Murphy,²² Heath²³ and Ordway *et al.*²⁴ failed to note a disappearance of achylia after liver therapy.

There were 15 cases of pernicious anemia in the series. All had a true achylia gastrica, even on reëxamination after the institution of specific therapy. We have never observed a case of Addisonian anemia in which a true achylia gastrica was not present. In borderline cases we feel that the presence of acid or enzymes in the stomach rules out a diagnosis of primary anemia.

Case Reports. CASE 1.—One of the patients included in this report entered the Hospital with the typical picture of a primary anemia. The erythrocytes were 1,100,000 and the hemoglobin too low to estimate. He had the typical pallor and an atrophic glossitis. The spleen was palpable and signs and symptoms of a combined lateral sclerosis were present. The first gastric analysis showed no free acid or rennet. A provisional diagnosis of Addisonian anemia was made. However, the blood studies revealed a low color and volume index and a microcytosis. The gastric analysis was repeated with histamin and gastric rennet was recovered. The patient is improving steadily on nonspecific therapy without liver.

We found no evidence of gastritis in any case of pernicious anemia. Invariably the stomach was "clean." Naturally one cannot assume that the achylia did not originate as a gastritis. However, the familial incidence of pernicious anemia and the inability to find any evidence of gastritis suggest the occurrence of the achylia as an inherited trait which may not develop until later life.

Combined Lateral Sclerosis. Vanderhoof²⁵ feels that achylia gastrica is as constant a finding in acroparesthesia as it is in per-

nicious anemia. There are not enough case reports based upon conclusive evidence of the existence of achylia to warrant the acceptance of this view at present. There were but 5 cases of definitely established posterior lateral sclerosis in this series. Only 2 had a true achylia, 1 of which had pernicious anemia. Our finding of gastric rennet in 3 cases following histamin would indicate that true achylia is not necessary to the diagnosis.

Incidence of Anemia (Not Primary) in Achlorhydria and Achylia Without Obvious Cause. Davies and James²⁶ recorded the incidence of anemia in 32 normal people with achlorhydria, over 60 years of age. In a group of 14 cases without acid response to histamin, 7 had erythrocyte counts under 4,000,000 and hemoglobin less than 60 per cent. The lower the pepsin concentration the greater was the tendency toward anemia. In a second group of 13 cases with acid response to histamin only 3 cases showed a similar degree of anemia. Blood counts were performed on 119 of our cases in which there was no obvious cause for anemia. The erythrocytes were under 4,000,000 and the hemoglobin less than 60 per cent in 7 of 22 cases of true achylia and in 20 of 97 cases of achlorhydria. It is noteworthy that the tendency toward anemia in true achylia was much greater than in achlorhydria.

Gastritis. The gastric residuum was routinely examined for evidence of gastritis. If gastritis was suspected an astringent lavage of zinc chlorid and formalin was given. A record was made of the amount of gross mucus and the sediment examined microscopically for mucus, pus, bacteria and tissue fragments. If these elements were present in excess and could be identified as having originated in the stomach a diagnosis of gastritis was made. Of our cases 41 (28 male and 13 female) were so classified (19.5 per cent). Six cases were diagnosed gastric lues. In 5 of these a gastric defect was present by Roentgen ray; a provisional diagnosis of luetic gastritis was made in the sixth. In this case, 5 gastric analyses were performed over a period of 2 years, during which time luetic therapy was administered. Each analysis showed an achlorhydria (rennet present) after histamin. An ordinary gastric analysis after 3 years of therapy showed a return of free acid up to 35. Such a return of free acid which has been consistently absent after histamin injection over a period of 3 years is unique in our experience. Tertiary lues without gastric defect was present in 3 other cases. We feel with Wile²⁷ that a catarrhal gastritis in luetic patients with achlorhydria may represent the first stage of gastric syphilis. Response to antiluetic therapy in some cases confirms this view. Alcohol was a probable etiologic factor in 13 cases (32 per cent). Foci of infection in the mouth, nose and throat are thought by Hurst²⁸ and others to be an important causative factor in gastritis. Definite evidence of such infection was present in 24 cases (59 per cent). The site of infection was as follows: teeth 13 cases; tonsils

11 cases; advanced pyorrhea 9 cases; sinuses 3 cases and the nasopharynx 1 case. Multiple foci were not uncommon.

There was definite disease of the heart, kidneys or bloodvessels in 10 cases (24 per cent). Degenerative disease of the cardiovascular-renal apparatus is not infrequently associated with gastritis, offering one explanation for the gradually increasing incidence of achlorhydria up to the seventh decade. The reason for the decreasing incidence of achlorhydria after this age may very well be the exodus of such patients before the eighth decade.

Only 12 per cent of our cases with gastritis had a true achylia. Hurst²⁹ recovered free acid in 50 per cent of his cases of achlorhydria merely by repeating the examination after gastric lavage. He feels that this is accomplished by ridding the mucosa of adherent mucus which retards gastric secretion. We have confirmed his findings in a few cases. However, we do not feel with him that failure to recover acid or enzymes after this procedure is proof positive of constitutional achylia or primary atrophic gastritis. In 12 cases with gastritis an apparent achylia was found by ordinary gastric analysis. Histamin injection established a diagnosis of true achylia in 5 of them. Five were converted into achlorhydria, 1 into hypochlorhydria and 1 became a normal acidity after injection of histamin. Most cases of apparent achylia showing evidence of gastritis by examination of the residuum after ordinary gastric analysis will be found capable of gastric secretory response after appropriate stimulation or treatment. The incidence of anemia in the gastritis group was less than in that found in cases of achlorhydria without gastritis.

Duodenitis. Hurst mentions the frequency of duodenitis in cases of achlorhydria. Knott³⁰ feels that increased alkalinity of the intestinal contents in achlorhydria allows bacteria which are confined normally to the colon to ascend to the small intestine or even to the stomach. A considerable experience with cultures of bile obtained through a duodenal tube suggests to us another possible explanation for the finding of colon organisms in the duodenum in achlorhydria. It seems likely that normally many organisms are withdrawn from the portal stream by the liver and excreted in the bile without actually infecting the biliary tract. Normally they are destroyed in the duodenum by acid influx, but when the duodenal content is constantly alkaline, an implantation of organisms may readily occur. From duodenal cultures of 10 cases, a colon bacillus was recovered in 5 instances and a *Streptococcus hemolyticus* in association with a *B. coli* in another. By examination of the duodenal aspirate 82 per cent of cases of gastritis and 58 per cent of cases of the entire series showed evidence of a catarrhal duodenitis. This suggests that the gastritis itself is a factor of importance in the development of duodenitis in cases of achlorhydria.

Syphilis. Of 210 cases of achlorhydria 22 had tertiary lues (10.5 per cent). There were 9 cases in which gastric lues was suspected; in 2 others cerebrospinal involvement was present; 4 cases had a true achylia. Antiluetic treatment brought about an apparent improvement in gastric secretory function in 6 cases of achlorhydria by the appearance of acid after treatment. Achlorhydria is generally present in luetic gastritis and the "diffuse fibrosis" type of gastric lues. However, in cases of gastric ulcer³¹ and pyloric stenosis which fulfill the established criteria for gastric syphilis, achlorhydria may not be present. When present in association with a lesion resembling ulcer the possibility of lues must always be considered.

Gastric Carcinoma. Hurst³² believes that the achlorhydria which occurs in over one-half the cases of gastric cancer is not the result of the growth but due to an antecedent chronic gastritis. He considers gastritis the most common predisposing cause of cancer. He has never observed the development of achlorhydria in a case of gastric cancer in which hydrochloric acid was present at the onset. One patient in this series with a pyloric carcinoma had a fasting hyperacidity (hydrochloric 90, total acidity 115); 3 months later an achlorhydria was present with a total acidity of 65. The diagnosis was confirmed at operation. Both Hurst and Porges³³ report that development of carcinoma in patients known to have had achlorhydria previously. Hurst attempts to classify cases of gastric cancer into 2 groups: those with persistent gastric acidity and those with achlorhydria. The latter type is termed by him "gastritis-cancer," namely, cases with achlorhydria due to chronic gastritis and usually having a short history. He supports this contention by quoting Hartman,³⁴ who found 44 per cent of 39 cases of cancer with achlorhydria alive 5 years after gastrectomy and only 22 per cent of 41 cases with acid alive 5 years after resection. Hurst argues that if achlorhydria resulted from the cancer the cases without acid should have a poorer prognosis. He further mentions Orator's³⁵ finding of a diffuse atrophic gastritis involving the fundus as well as the pyloric region in 19 of 20 such cases. Hurst stresses the importance of a universal atrophic gastritis in the etiology of so-called "primary" cancer, which he feels should be called "gastritis-cancer."

We found 16 cases of gastric carcinoma in this survey of 210 cases of achlorhydria. Only 4 of them had an apparent achylia after ordinary fractional analysis; histamin was not used. The remainder were cases of apparent achlorhydria. In 10 of these the total acidity reached a high level of 25 or more. The achlorhydria of gastric carcinoma is characteristically associated with a high total acidity due to the presence of organic acid. The theory of Hurst is deserving of serious consideration to account for the large number of cases of cancer with achlorhydria. We are frequently

at a loss to explain the presence of achlorhydria in a patient with a small carcinoma in the region of the pylorus. However, the explanation is not any more obscure than an attempt to account for the achlorhydria which sometimes develops after resecting only a small portion of the distal end of the stomach. Crohn³⁶ believes that some disturbance of the innervation of the stomach probably accounts for the latter condition. It is obvious from a survey of our cases that an achlorhydria may be associated with any type of cancer anywhere in the stomach. That the achlorhydria may have antedated the malignancy in many cases cannot be denied.

It should be borne in mind that many cases of gastric carcinoma have considerable free acid and some an actual hyperacidity. Two of us³⁷ recently reported 3 cases in which ulcer and cancer of the stomach occurred independently, the cancer in each case involving the pylorus and the ulcer being higher up on the lesser curvature with normal mucosa intervening. All 3 had a very high gastric acidity.

Gall Bladder Disease. Cholelithiasis was formerly considered by many to be one of the more common lesions associated with achlorhydria. This has not been our experience. A fractional gastric analysis was performed on 62 cases of cholelithiasis proved by operation.³⁸ Hyperacidity was encountered in 32, normal acidity in 14, hypoacidity in 13, and achlorhydria in only 1 case. Only 7 cases of cholelithiasis (3 per cent) were found in this series of 210 cases of achlorhydria. True achylia was not encountered. A clinical diagnosis of cholecystitis was made in 16 cases. Most of them were not operated upon and the diagnosis was not confirmed. The incidence of achlorhydria was no greater in these cases of gall-bladder disease than it is in any like group of individuals of the same age and sex.

Visceroptosis. A clinical diagnosis of visceroptosis was made in 21 females and 2 males (11 per cent). The constitutional habitus was recorded in 164 cases; 78 (48 per cent) were asthenic; 61 (37 per cent) were sthenic and only 25 cases (15 per cent) were hypersthenic. The inference may be drawn that achlorhydria is more frequent in the *habitus asthenicus* and is very infrequent in people of the hypersthenic build. The presence of achlorhydria in a patient of hypersthenic habitus would appear to be of more clinical significance.

Colitis. Twenty-two patients had signs and symptoms of excessive spasticity of the colon, and so-called spastic or irritable colon. Seven had mucous colitis and 2 ulcerative colitis. Functional or organic disease of the colon was noted in 30 cases (14 per cent). In a series of 45 cases of mucous colitis recently analyzed³⁹ hypochlorhydria was present in 11 and achlorhydria in but 2 cases. Apparently achlorhydria is not any more frequent in colitis than in a similar group of normal individuals of the same age and sex.

Cardiovascular-renal Disease. Disease of the heart, kidneys or bloodvessels was noted in 35 cases (17 per cent), a normal incidence for patients in this age group. These cases were distributed as follows: arteriosclerosis 10 cases, hypertension 10 cases, nephritis 4 cases and heart disease 11 cases.

Chronic Arthritis. Faber⁴⁰ reported the presence of achylia in 15 of 65 cases of polyarthritis. In an analysis of 250 cases of arthritis, Miller and Smith⁴¹ found achlorhydria and hypochlorhydria 5 times more frequently than in normal individuals. Lottrup⁴² found that 44 per cent of his cases of chronic progressive polyarthritis had achylia. Chronic arthritis was noted in only 8 of 210 cases of achlorhydria in this series.

Dermatoses. In a survey of 12 cases of acne rosacea by Ryle and Barber,⁴³ achlorhydria was encountered 5 times and hypochlorhydria twice. Brown⁴⁴ analyzed 50 cases of acne rosacea and found achlorhydria in 7 and hypochlorhydria in 8 cases. We encountered only 1 case of acne rosacea and 3 of chronic eczema in the series.

Other Diseases. Not a single case of proven duodenal ulcer was noted in the series. There was, however, 1 case of gastric ulcer: it occurred in an untreated luetic negro with symptoms of only 1-year duration who was suspected of having carcinoma. At operation a large ulcer was found on the posterior wall of the stomach in the antrum. The pathologist failed to find evidence of cancer or any definite evidence pointing toward its luetic origin. This patient did not have a true achylia (enzymes present after histamin).

Gastrogenous Diarrhea. Diarrhea was present in 33 of 210 cases with achlorhydria. In 21 cases (10 per cent) other causes could be ruled out, and the diarrhea was apparently dependent upon the achlorhydria and responded to acid or gastritis therapy. True achylia was found in only 2 of the 21 cases. Gastrogenous diarrhea does not occur more frequently in association with true achylia than with achlorhydria. Only 1 of 15 cases of pernicious anemia had gastrogenous diarrhea. Six cases showed definite evidence of gastritis. Five patients were alcoholics. Gastrogenous diarrhea invariably responds to acid therapy. In 16 cases, which were followed, the diarrhea could be controlled but usually showed a tendency to recur if acid were stopped. It was found necessary to use as much as 8 cc. of dilute hydrochloric acid after each meal to control the diarrhea in some patients with alcoholic gastritis.

Gastric Evacuation Time in Achlorhydria. The time of gastric evacuation of the test meal was routinely recorded. Both clinicians and roentgenologists have noted a tendency toward rapid stomach emptying in achlorhydria. In 87 of 210 cases (41.4 per cent) the stomach emptied the test meal more rapidly than normal. Rapid gastric emptying was more common in true achylia (57 per cent as compared with 38 per cent in achlorhydria). The element of infection or of inflammation of the mucosa does not seem to be the factor

responsible for rapid gastric evacuation time, since only 41 per cent of cases with gastritis showed rapid emptying. Gastrogenous diarrhea did not occur more often in association with rapid stomach emptying (43 per cent) than in normally emptying stomachs. An observation of significance is the remarkable constancy of the rate of stomach emptying in the cases in which several gastric analyses were performed. Bell and MacAdam⁴⁵ found this to be true of normal individuals. Our study confirms this finding in patients with achlorhydria.

Constipation and Achlorhydria. Constipation was severe enough to be listed as one of the diagnoses in 71 of 210 cases of achlorhydria (34 per cent). It occurred $3\frac{1}{2}$ times more often in achlorhydria than did gastrogenous diarrhea. It is unlikely, however, that the incidence of constipation is any more common in patients with achlorhydria than in other patients of similar age and sex. Constipation occurred just as frequently as gastrogenous diarrhea in the patient with rapid evacuation time. In 32 of the 71 cases of constipation the gastric emptying time of the test meal was too rapid.

Incidence of Focal Infection in 210 Cases of Achlorhydria. Obvious focal infection in the mouth was present in 98 of 210 cases (47 per cent). The foci were distributed as follows: teeth, 64 cases; tonsils, 41 cases; pyorrhea, 33 cases; and sinusitis, 8 cases. Foci of infection were found more frequently in association with gastritis (59 per cent as compared with 44 per cent). Since many of the cases of achylia and of true achlorhydria may have resulted from gastritis even though evidence of it cannot be obtained, the ablation of all foci of infection is undoubtedly important. The administration of hydrochloric acid in these cases takes on an added importance, at least until foci can be removed, as a prophylactic against the implantation of infection in the stomach and small bowel.

Summary. In a review of 210 cases of achlorhydria in patients with gastrointestinal complaints, it appears that the incidence of achlorhydria is greater in normal patients (in Vanzant's study, 12.1 per cent) than in patients who consult a physician for gastrointestinal complaints (5.7 per cent). It is more frequent in females and its incidence increases with age up to the seventh decade. No essential difference was found in the age incidence of true achylia and of achlorhydria.

The ordinary fractional gastric analysis is compared with the histamin gastric analysis in 64 cases. Forty per cent of cases of apparent achylia show either acid or enzyme secretion after histamin injection. Evidence is presented pointing toward the gradual development of secretory insufficiency; a complete permanent achylia probably does not occur suddenly.

The term "true achylia" should be used only when both hydrochloric acid and gastric ferments are absent throughout the period of a fractional gastric analysis which follows an injection of an ample

dose of physiologically potent histamin. The condition is practically always permanent. The status of gastric secretion as determined by histamin represents the maximum of gastric secretory work and can rarely be improved in spite of treatment of the underlying cause.

The significance and incidence of various diseases and symptoms which are commonly thought to be associated with achlorhydria are discussed. In 15 cases of *primary anemia* all had a true achylia; no return of acid after specific therapy was noted. We found no evidence of gastritis in any case and doubt if it is a frequent etiologic factor in the achylia of primary anemia. We feel that a true achylia gastrica is necessary to a diagnosis of Addisonian anemia.* In some cases at least the achylia precedes the development of anemia by many years. The achylia is probably the result of an inherited trait which does not manifest itself until later in life. The incidence of secondary anemia in our cases is considerably greater in true achylia than in achlorhydria.

Gastritis was noted in 19.5 per cent of the cases of achlorhydria. Foci of infection, alcohol, lues and cardiovascular-renal disease seemed to be of most importance in its etiology. In most cases of gastritis a secretory response follows repetition of the analysis after gastric lavage (Hurst) or histamin injection. Catarrhal duodenitis is a very frequent accompaniment of achlorhydria (50 per cent) but occurs more frequently if gastritis is also present (82 per cent).

We found *tertiary lues* more common in the cases of achlorhydria than its occurrence in a similar group of patients without achlorhydria. The significance of achlorhydria in gastric lues is discussed.

Carcinoma of the stomach was found in 16 cases. True achylia is rare, but achlorhydria is quite common in gastric cancer. The relationship which gastric acidity bears to the etiology of gastric cancer is discussed.

Contrary to prevalent opinion we found that the incidence of achlorhydria was no greater in cases of *gall-bladder disease* or *colitis* than it is in any group of individuals of the same age and sex.

The *constitutional asthenic habitus* of Stiller was present to some degree in 48 per cent of cases. The *habitus hypersthenicus* was so infrequent that its existence with achlorhydria should suggest a possibility of some underlying acquired pathologic condition.

Gastrogenous diarrhea occurred in 10 per cent of patients. It was not more frequent in association with achylia than with achlorhydria. Alcoholism and gastritis seemed to be factors of some importance in the production of the diarrhea.

Constipation was a major complaint in 34 per cent of cases, occurring $3\frac{1}{2}$ times more often than diarrhea.

* This statement must be modified in view of Castle's recent reports. The so-called "specific stomach factor" may be absent in rare instances without there being an associated achylia. We have encountered 1 case of this type recently.

Rapid stomach emptying, present in 41 per cent of cases of achlorhydria, was decidedly more common in true achylia. Gastritis apparently was not a factor. When several analyses were carried out on the same patient, there was a remarkable constancy in the rate of stomach emptying. That rapid gastric evacuation *per se* is not the important cause of gastrogenous diarrhea is indicated by an equal frequency of rapid emptying in cases with constipation.

The incidence of foci of infection and the importance of their ablation in cases of achlorhydria is stressed.

BIBLIOGRAPHY.

1. Rehfuess, M. E.: *Am. J. Med. Sci.*, 1914, 147, 848.
2. Eggleston, E. L.: *J. Am. Med. Assn.*, 1924, 33, 260.
3. Popielski, L.: *Arch. f. d. ges. Physiol.*, 1920, 178, 214.
4. Carnot, P., Koskawski, W., and Liebert, E.: *Compt. rend. Soc. de Biol.*, 1922, 86, 575.
5. Gompertz, L. M., and Voorhaus, M. G.: *J. Lab. and Clin. Med.*, 1925, 11, 14.
6. Bockus, H. L., and Bank, J.: *Arch. Int. Med.*, 1927, 39, 508.
7. Wright, C. B.: *Arch. Int. Med.*, 1924, 33, 435.
8. Bennett, T. I., and Ryle, J. A.: *Guy's Hosp. Rep.*, 1921, 71, 286.
9. Vanzant, F. R.: *Proc. Staff, Mayo Clinic*, 1931, 6, 297.
10. Conner, H. M.: *Proc. Staff Mayo Clinic*, 1929, 4, 200.
11. Gaither, E. H.: *Proc. Am. Gastro-enterological Assn.*, 1931. (Unpublished).
12. Gilman, A., and Cowgill, G. R.: *Am. J. Physiol.*, 1931, 97, 124.
13. Vineberg, A. M., and Babkin, B. P.: *Am. J. Physiol.*, 1931, 97, 69.
14. Cahn, A., and v. Mehring, J.: *Deut. Arch. f. klin. Med.*, 1886, 39, 233.
15. Levine, S. A., and Ladd, W. S.: *Bull. Johns Hopkins Hosp.*, 1921, 32, 958.
16. Grinker, R. R.: *Arch. Int. Med.*, 1926, 38, 292.
17. Faber, K.: *Berlin klin. Wehnschr.*, 1913, 1, 958.
18. Hurst, A. F.: Quoted by Levine and Ladd.
19. Sturtevant, M.: *J. Am. Med. Assn.*, 1925, 85, 1638.
20. McPeak, E. M., and Neighbors, DeW.: *Southern Med. J.*, 1927, 20, 926.
21. Johansen, A. H.: *J. Am. Med. Assn.*, 1929, 92, 1728.
22. Minot, G. R., and Murphy, W. P.: *J. Am. Med. Assn.*, 1927, 89, 759.
23. Heath, E. H.: *J. Am. Med. Assn.*, 1928, 91, 928.
24. Ordway, T., and Gorham, L. W.: *J. Am. Med. Assn.*, 1928, 91, 925.
25. Vanderhoof, D.: *Arch. Int. Med.*, 1923, 32, 958.
26. Davies, D. T., and James, T. G. I.: *Lancet*, 1930, 2, 899.
27. Wile, U. J.: *Arch. Dermat. and Syph.*, 1920, 1, 543.
28. Hurst, A. F.: *Proc. Royal Soc. Med.*, 1931, 24, 447.
29. Hurst, A. F.: *Lancet*, 1929, 2, 1023.
30. Knott, F. A.: Quoted by Hurst (29).
31. Bockus, H. L., and Bank, J.: *J. Am. Med. Assn.*, 1928, 90, 175.
32. Hurst, A. F.: *Lancet*, 1929, p. 1024.
33. Porges: Quoted by Hurst (29).
34. Hartman: Quoted by Hurst (29).
35. Orator, V.: *Virch. Arch.*, 1925, 256, 202.
36. Crohn, B. B.: *Affections of the Stomach*, W. B. Saunders Company, Philadelphia, 1927.
37. Bockus, H. L., and Bank, J.: *Med. Clin. No. Am.*, 1931, 14, 869.
38. Bockus, H. L., Shay, H., Willard, J. H., and Pessel, J. F.: *J. Am. Med. Assn.*, 1931, 96, 311.
39. Bockus, H. L., Bank, J., and Wilkinson, S. A.: *Am. J. Med. Sci.*, 1928, 176, 813.
40. Faber, K.: *Berlin klin. Wehnschr.*, 1913, 50, 958.
41. Miller, S., and Smith, F. B.: *Quart. J. Med.*, 1927, 20, 271.
42. Lottrup, M.: *Hospitalstidende*, 1929, 72, 977.
43. Ryle, J. A., and Barber, W. O.: Quoted by Wilkinson and Brockbank: *Quart. J. Med.*, 1931, p. 219.
44. Brown, W. H.: *Brit. J. Dermat. and Syph.*, 1925, 3, 213.
45. Bell, J. R., and MacAdam, W.: *Am. J. Med. Sci.*, 1924, 167, 520.

TRANSIENT COMPLETE BUNDLE-BRANCH BLOCK.

BY ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE,

AND

JOHNSON MCGUIRE, M.D.,

INSTRUCTOR IN MEDICINE,

CINCINNATI.

(From the Department of Internal Medicine, University of Cincinnati.)

THE occurrence of bundle-branch block is fairly common, as electrocardiographic tracings have demonstrated. It is seen principally in patients with chronic heart disease and causes no characteristic symptomatology. King has described a reduplication of the apex thrust and a splitting of the first sound, by which its presence may be suspected, but the condition is recognized with certainty only through electrocardiographic records.

Complete bundle-branch block, coming on acutely in a patient without previous cardiac symptoms, has received scant notice in the literature. We have recently observed 2 patients in whom symptoms came on acutely, and in whom electrocardiographic tracings demonstrated a transient bundle-branch block.

Case Reports. CASE 1.—Mrs. X, white, aged 46 years, was seen in consultation with Dr. Frank Conroy March 25, 1931, at 11.30 P.M. About 1 hour previously, while riding horse-back, she collapsed. There was expectoration of a pink frothy sputum. Physical examination showed bubbling râles throughout both lungs. The patient was in a state of shock. There was pallor and the skin was cold and moist. The right heart was dilated, the sounds weak, regular and clear. The blood pressure was 90 systolic and 58 diastolic. The patient was given morphin, $\frac{1}{2}$ grain and adrenalin (1 to 1000), 10 minims. The adrenalin was repeated twice before the patient was taken to the hospital at 1.30 A.M. By morning there were only a few râles present. The blood pressure had risen to 120 systolic and 76 diastolic. An electrocardiographic tracing (Fig. 1) showed a right* bundle-branch block. The symptoms cleared up completely within 48 hours. At no time was there pain or fever, and the leukocyte count was normal. A second electrocardiographic tracing 4 days later (Fig. 2) gave no evidence of bundle-branch block. The Wassermann test was negative, and the history gave no indication of lues. There had been no previous cardiac symptoms. There was no history of rheumatic fever. No evidence of thyroid disease was found. The clinical diagnosis was acute bundle-branch block, acute pulmonary edema. The physical signs over the heart did not suggest bundle-branch block.

CASE 2.—The patient, a white female, aged 51 years, was admitted to the Surgical Service of the Cincinnati General Hospital, January 29, 1931, with the complaint of nausea, vomiting, and pain in the right upper quadrant of the abdomen. A mass was palpable in this region, and an explora-

* The usual conventional standards have been employed in identifying right bundle-branch block.

tory laparotomy performed. The mass was found to be a greatly scarred right lobe of the liver covered by a white thickened capsule. The gall bladder was obviously diseased, although containing no stones, and was removed, and the wound drained.

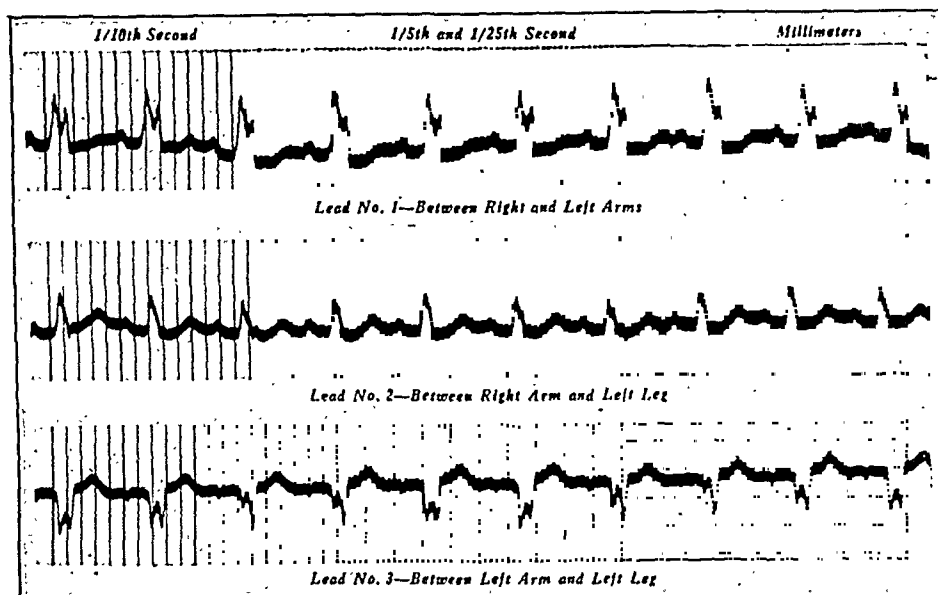


FIG. 1

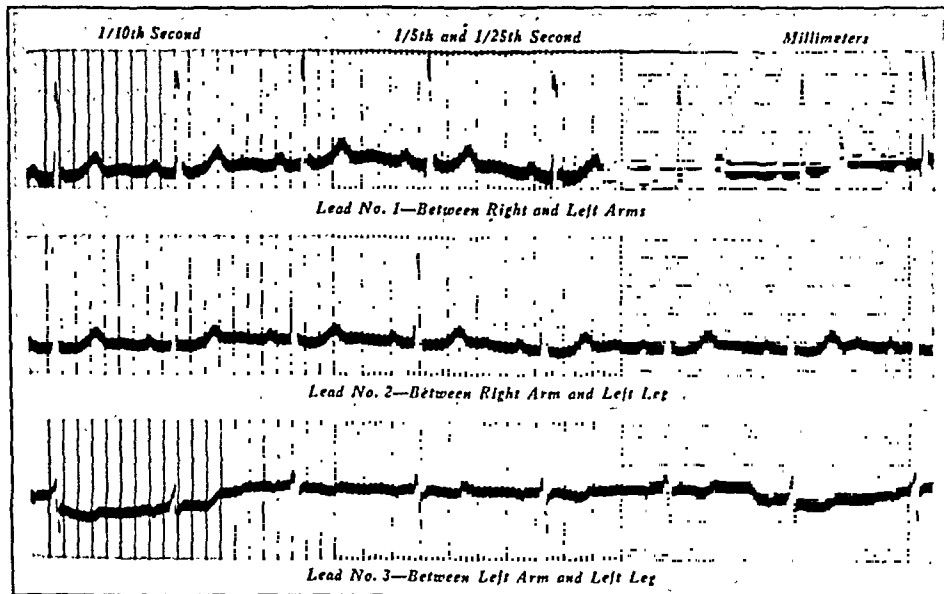


FIG. 2

Convalescence was slow and complicated by some infection of the wound, a low-grade fever, and the development of ascites.

At this point it should be mentioned that on admission the heart showed nothing of interest except for a soft systolic murmur at the apex. There was a slight hypertension. The blood pressure was 158 systolic and 98

diastolic. Relative cardiac dullness was 3 by 9 cm. The pulse was regular. Laboratory data before and after operation were of no significance except for the presence of a positive blood Wassermann test.

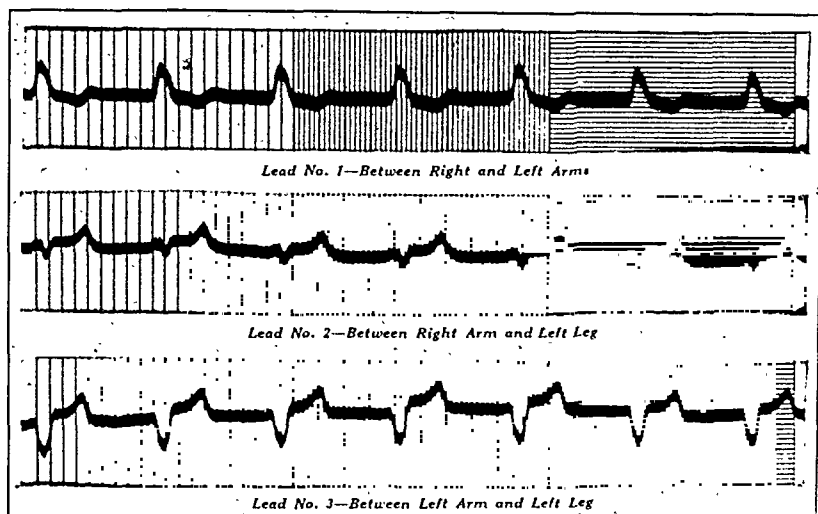


FIG. 3

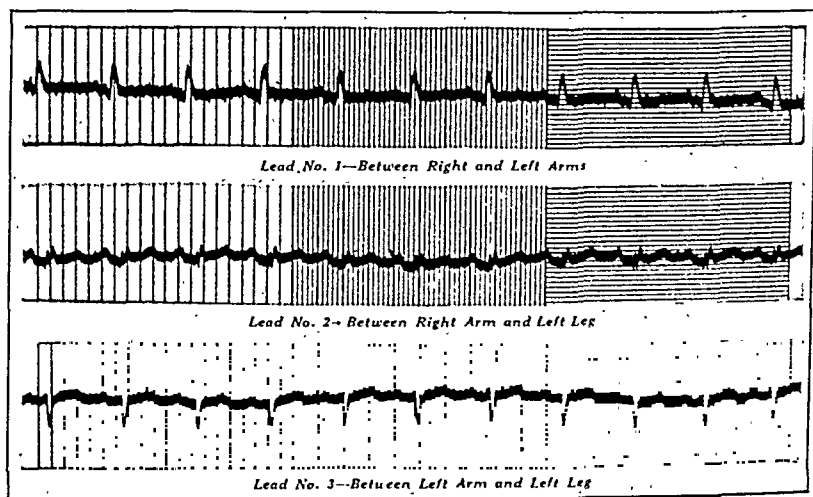


FIG. 4

On March 10, the pulse rate suddenly dropped from an average rate of 140 to 60, and simultaneously the patient went into a condition of shock. There was definite air hunger, slight cyanosis of the nail beds and lips, pallor, sweating, profound exhaustion, and a temperature of 95° F.

The pulse was regular, of low tension, the blood pressure 70 systolic and 40 diastolic, and the rate 68. The veins of the neck were somewhat distended and there was slight pretibial edema. There was no visible apical

impulse; percussion indicated slight enlargement to the left and right. No shock or thrill was noted. No gallop rhythm or splitting of the first heart sound was heard. A loud rough apical systolic murmur was present.

An electrocardiogram (Fig. 3) was taken at once which showed right bundle-branch block. No "P" waves were discernible, but there was no irregularity and the rate was only 70. Nodal rhythm (Type II) was suspected, and additional support for this impression was afforded by a record made with needle electrodes and thoracic leads, which showed neither "P" waves nor the oscillations associated with auricular fibrillation.

The usual treatment for shock was instituted—caffein, adrenalin, and small amounts of hypertonic glucose intravenously. Gradual improvement ensued, the symptoms of shock lasting only 3 days.

Subsequently there has been no marked general change for the better. Weakness, ascites, and some edema of the ankles continue to be present, and the liver has increased in size and is nodular and indurated.

However, rather significant alterations have appeared in the electrocardiogram. A record of April 20 (Fig. 4) showed disappearance of the bundle-branch block with restoration of normal sinus rhythm. There was, however, low voltage, slight widening and slurring of the "Q-R-S" complexes in all leads.

Discussion. Wolff, Parkinson and White report the occurrence of transient bundle-branch block associated with paroxysmal tachycardia in children and young adults.

In the cases reported in this paper, cardiac symptoms developed acutely in patients who had previously been free from circulatory disturbances. In one there was an acute pulmonary edema. This patient was apparently in perfect health. A few hours after the onset of the pulmonary edema, complete bundle-branch block was demonstrated. The symptoms cleared up completely, and the bundle-branch block disappeared. In our review of the literature, we have not seen *transient complete* bundle-branch block emphasized. That profound disturbances may be associated with it is shown by the occurrence of acute circulatory failure in the 2 cases reported. Willius and Keith report 2 similar cases of acute pulmonary edema with transient *incomplete* bundle-branch block.

What the nature of the lesion in the bundle-branch tissues may be is not at all clear. Whatever it is, it produces only temporary interference in the function of the conducting system. In Case 1, a complete study failed to reveal any evidence of organic disease, aside from the findings reported in the abstract. The absence of pain, fever, leukocytosis and friction rub, eliminate a coronary occlusion in our patients.

While we have no definite proof, we believe it reasonable to assume that the occurrence of acute symptoms coincided with the development of bundle-branch block.

BIBLIOGRAPHY.

1. King, J. T.: The Clinical Recognition and Physical Signs of Bundle-branch Block, *Am. Heart J.*, 1928, 3, 505.
2. Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle-branch Block, *Am. Heart J.*, 1926-1927, 2, 255.
3. Wolff, L., Parkinson, J., and White, P. D.: Bundle-branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am. Heart J.*, 1930, 5, 685.

**ARTERIOLAR STUDIES IN PATIENTS WITH HYPERTENSIVE
HEART DISEASE WITHOUT HYPERTENSION.***

By EMMET F. HORINE, M.D.,

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE

MORRIS M. WEISS, M.D.,

CLINICAL ASSISTANT IN MEDICINE

AND

MARION F. BEARD, M.D.,

RESIDENT PATHOLOGIST, LOUISVILLE CITY HOSPITAL, LOUISVILLE, KY.

(From the Divisions of Medicine and Pathology, School of Medicine, University of Louisville.)

THE association of diffuse arteriolar sclerosis and essential hypertension can no longer be questioned. Numerous investigators^{1,2,3} have definitely identified the histologic nature of the characteristic lesion in this disease and its widespread distribution throughout the body. Diffuse arteriolar sclerosis is pathognomonic of persistent hypertension. The arteriolar sclerotic or primary contracted kidney, for example, always evidences a present or previous hypertensive state.

Recently Kernohan, Anderson and Keith⁴ have been able to demonstrate the same distinctive histologic changes in the arterioles of the voluntary muscles of ambulatory patients with diffuse hypertensive cardiovascular disease as are found at autopsy. After determining the ratio of wall to lumen in the vessel of normal individuals as a standard, the marked narrowing of the lumen of the arterioles in essential hypertension was shown quantitatively. They found that in the normal the average ratio of vessel wall to lumen is 1 to 2, with variations from 1 to 1.7 to 1 to 2.7, whereas the average ratio for the arterioles of the hypertensive patients was 1 to 1.4 in cases of benign hypertension and 1 to 1.1 in cases of severe benign and malignant hypertension.

It occurred to us that similar biopsy studies might be of confirmatory value in the diagnosis of a phase of cardiac disease which we designate "hypertensive heart disease without hypertension,"⁵ although it is recognized that the ratios have only relative value on account of various uncontrolled variables in the preparation of the specimen. Not infrequently individuals are encountered who have cardiac enlargement with normal or low blood pressure but no organic valvular lesion, adhesive pericarditis, severe anemia or other recognized cause for the enlargement. Even though the former level of the blood pressure is unknown, convincing clinical or path-

* Read before the Central Society for Clinical Investigation, Chicago, Illinois, November 20, 1931.

ologic evidence of a preëxisting hypertension can always be found. Aside from the otherwise unexplained cardiac hypertrophy these patients may show impairment of renal function or even uremia, a suggestive roentgenologic cardiac silhouette, coronary types of electrocardiograms as are so often found in the known hypertensive individuals, ophthalmoscopic signs of known hypertension, and finally autopsy discloses diffuse arteriolar sclerosis which always evidences a persistent hypertension during the life of the individual.

Because of the normal or reduced pressure found when first examined, these patients frequently are classified wrongly. If an apical systolic murmur is present a diagnosis of mitral insufficiency is made. If a murmur at the base is heard some other valvular diagnosis follows, while if no murmur is audible the diagnosis may be "chronic myocarditis" or some other equally obscure entity. The American Heart Association⁶ merely suggests that these persons be placed in the group of unknown etiology. The actual and alarming frequency of hypertensive states is undoubtedly obscured to a great degree because of such wrong classifications.

Our present study includes biopsies performed on 11 individuals with cardiac enlargement but normal blood pressure and no other factor to explain the cardiac enlargement. The method and histologic technique pursued was similar to that of Kernohan, Anderson and Keith⁴ on the known hypertensive individuals. Under local anesthesia small pieces of the deltoid muscle were removed. These specimens were submitted to the pathologic laboratory along with controls but without the clinical histories, so that the findings should be unbiased.

Tissues were fixed in Zenker's fluid, embedded in paraffin, cut at 7 micra and stained with hematoxylin and eosin. Those showing various stages of thickening of the vessel walls were also stained with Mallory's connective-tissue stain and osmic acid.

Arterioles, vessels measuring from 30 to 100 micra in outside diameter and cut at right angles, were selected. Measurements were made with a Bausch & Lomb ocular micrometer. The wall and lumen of each vessel were measured twice at right angles and averaged. The ratio consists, then, of the average thickness of the wall found by measuring it four times at right angles to the average diameter of the lumen found by measuring it twice at right angles. Three to five arterioles were measured in each case.

A summary of the clinical and pathologic data is shown in the accompanying table. Some of the patients came to the medical out-patient department. The others were observed in the wards of the hospital. The ages ranged from 41 to 88 years. All gave a history of the anginal or congestive type of heart failure of many months' duration. Suggestive roentgenologic, electrocardiographic and ophthalmoscopic evidences of a preëxisting hypertension were present. Three of the patients died shortly after the biopsies were

TABLE 1.—ANALYSIS OF DATA OF 11 CASES WITH BIOPSY.

Pathology Lab. No.	Sex.	Race.	Age.	History.	Wassermann.	Blood pressure.	N.P. nitrogen.	Roentgen ray; cardiothoracic ratio.	Electrocardiogram.	Ophthalmoscopic picture.	Ratio of arterioles to lumen.
30-663	M.	White	76	Symptoms for 18 years, leads a very restricted life. Has dyspnea and substernal pain on exertion	Negative	120/85 mm. Hg.	27.9 mg. per 100 cc. blood	15.5:29 cm. Aorta widened	Auricular fibrillation; ventricular premature contractions; slurred Q-R-S and low voltage	Tortuosity and thickening of arterioles	1:0.95
30-670	M.	White	70	Symptoms for 4 years, leads a restricted life. Has dyspnea on exertion and edema of feet and ankles	Negative	120/76	35.4 mg.	18:28 cm. Marked cardiac enlargement	Bundle branch block	Negative	1:0.85
30-661	M.	Negro	56	Right hemiplegia 4 years ago. Symptoms of heart failure date back 18 months. Leads a restricted life	Negative	130/80	18.5:29.5 cm.	1:1.02
30-782	M.	Negro	66	Dyspnea and edema of lower limbs began 18 months ago	Negative	144/70	30 mg.	17.5:32.5 cm.	Auricular fibrillation; slurred Q-R-S and low voltage in all leads	Slight sclerosis of arterioles	1:0.70
30-671	F.	White	65	Symptoms of congestive heart failure for 2½ years. Leads a very restricted life	Negative	140/60	31.5 mg.	14.5:23 cm.	Auricular premature contractions; T-I + T-II inverted, slight slurring of Q-R-S	Disks blurred, sclerosis of arterioles	1:0.83
30-707	M.	Negro	41	Congestive heart failure for past 18 months. Left hospital slightly improved. Died suddenly a few weeks later	+++	120/70	35 mg.	17.5:26.5 cm. Aorta widened	1:0.73
30-708	M.	Negro	73	Symptoms of congestive failure for past 18 months	++	118/82	31 mg.	15:28 cm. Aorta widened	T-II inverted, Q-R-S widened in all leads	Arterioles tortuous	1:1.31
30-747	M.	Negro	88	Weakness and dyspnea for past several years. Edema of lower limbs. Recently substernal pain and nocturnal dyspnea. See autopsy report	Negative	130/80	57 mg.	20:28 cm. Aorta markedly widened	Disks pale, arterioles tortuous	1:0.96
30-662	M.	Negro	52	Congestive failure for past year	Negative	130/86	26 mg.	15:27.5 cm.	T-I flattened, T-II isoelectric, deep Q-III, LAD. Low voltage, T-I isoelectric	Negative	1:1.23
30-832	M.	Negro	54	Dyspnea and edema for past 6 months	a/c	110/70	26 mg.	19:30 cm.	Low voltage and slurring of Q-R-S in all leads	Arterioles very tortuous	1:1.05
30-781	M.	Negro	50	Repeated admissions for congestive heart failure during past 4 years. Dead	++++	98/90	50 mg.	16:29.5 cm.		Arterioles very tortuous and thickened	1:0.88

performed. Only one autopsy was obtained. The ratio of wall to lumen in the cases ranged from 1 to 1.31 to 1 to 0.70. This corresponds to the average ratio of 1 to 1.4 to 1 to 1.1 found by Kernohan, Anderson and Keith⁴ in the known hypertensive individuals and is in marked contrast with the ratio of 1 to 2 found by them in normal controls and informally confirmed by us.

Pathology. The histologic changes were very similar to those described by Kernohan, Anderson and Keith in the known hypertensive patients. In most of the cases there were some changes in the skeletal muscle consisting of degeneration of the sarcoplasm. The sections showed occasional isolated muscle cells in which the cytoplasm was entirely granular, there being a loss both of the longitudinal and cross striations, and a loss in the staining power of the nuclei. Most of the specimens showed some fibrosis about the arterioles. This appeared more marked in those cases in which the normal wall-lumen ratio was most reduced. There was little lymphocytic infiltration in this fibrous tissue.

Studies of the arteriole walls showed the most characteristic and prominent change to be in the media. This change was evidenced by an increase in thickness of the media, and by an increase in the number of nuclei on cross-section. The muscle cells appeared to be increased in size, though this could not be proved with certainty. There was also definite thickening of the intima in all of the cases. This intimal thickening was less marked in those vessels showing the least disturbance of the normal wall-lumen ratio. The increased thickness of the intima was characterized chiefly by an increase in the internal elastic lamina. In the normal arteriole the internal elastic lamina is scarcely visible, but in the sections studied there was a definite thickening of this layer as shown by Mallory's connective-tissue stain. In our series there appeared to be very little, if any, proliferation of the lining endothelial cells. Studies of the tissues stained for fat with osmic acid failed to show any lipid infiltration. There was no evidence of deposition of calcium or processes of degeneration in the media in any of the sections.

The following case history and necropsy is illustrative of the clinical and pathologic findings in a patient with "hypertensive heart disease without hypertension:"

Case Report No. S 30-747.—Male, negro, aged 88 years, was admitted to the Louisville City Hospital on October 16, 1930, complaining of weakness and dyspnea of several years' duration. There had been progressive edema of the dependent portions of the body. During recent months attacks of nonradiating substernal pain were experienced and also frequent paroxysms of nocturnal dyspnea. Neither the family history nor that of previous illnesses was of importance.

Examination revealed an undernourished, senile, orthopneic negro whose palpable arteries were sclerosed and tortuous. The blood pressure was 130 systolic and 80 diastolic mm. Hg with the heart markedly enlarged. There was a loud blowing apical systolic murmur and a totally irregular

ination. When retinal changes once occur they persist as mute evidence of arterial hypertension, regardless of whether the pressure remains high or falls to subnormal levels. O'Hare and Walker¹² have shown that "the finding of retinal arteriosclerosis in patients with a normal or low blood pressure probably indicates the existence of a previous hypertension with subsequent myocardial weakening or loss of vascular tonus." Retinal changes alone may be sufficient for a diagnosis of hypertensive heart disease.

Master¹³ described the "high-voltage electrocardiogram" and the "hypertension roentgenogram" and claimed that they may be the only existing evidence of a previously long-standing hypertension. O'Hare, Calhoun and Altnow¹⁴ state that 81 per cent of their cases of "chronic myocarditis" with low blood pressure and characteristic retinal changes had typical or suggestive roentgenograms of the hypertensive heart.

Should it be impossible to make with certainty an antemortem diagnosis of a preëxisting hypertension from the cardiac enlargement, retinal findings, the electrocardiogram or the Roentgen ray, a biopsy may be performed. It permits an immediate diagnosis instead of a postponement of the diagnosis until autopsy findings are disclosed.

Arteriolar lesions were found in the deltoid muscle of all our cases. The frequency with which arteriolar lesions of the voluntary muscles was found by Kernohan, Anderson and Keith is far greater than that reported in the work of others. They comment on this and offer the possible explanation that previous investigators, perhaps, did not include cases of the serious progressive type of hypertension, such as those which they classed as cases of early malignant or malignant hypertension. More recently Barker, Keith and Kernohan,¹⁵ from a study of specimens obtained at biopsy from the pectoralis major muscle in more than 100 cases of hypertension have confirmed this work of Kernohan, Anderson and Keith. None of our biopsy cases had malignant hypertension. It is probable that marked and characteristic arteriolar lesions were found in every instance by us because our cases were "worn out" hypertensives. They undoubtedly had hypertension over a long period of time before coronary changes or myocardial failure reduced the level of the blood pressure.

Summary. 1. Biopsy specimens of the deltoid muscle were obtained from 11 individuals with cardiac enlargement but normal blood pressure and no other factor to explain the enlargement.

2. Histologic changes in the intima and media of the arterioles similar to those encountered in known hypertensives were found in all.

3. Careful measurements of the arterioles of the specimens gave a ratio of wall to lumen from 1 to 1.31 to 1 to 0.70, similar to ratios found in known hypertensives and in marked contrast to the normal ratio of 1 to 2.

4. Three patients are now dead and one autopsy was obtained in which a generalized arteriolar sclerosis was found.

5. The frequency with which hypertensives show arteriolar lesions of the voluntary muscles is discussed.

6. A diagnosis of "hypertensive heart disease without hypertension" may be confirmed by biopsy studies of the voluntary muscles.

NOTE.—We desire to express our sincere thanks to Dr. John Walker Moore, Dean, for his kind permission to make this study; to Dr. A. James Miller head of the Department of Pathology, for valuable suggestions and technical assistance; and to the resident staff, both medical and surgical, of the Louisville City Hospital for their interest and assistance.

REFERENCES.

1. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchow's Arch. f. Path. Anat.*, 1904, **178**, 367.
2. Evans, Geoffrey: A Contribution to the Study of Arteriosclerosis with Special Reference to its Relation to Chronic Renal Disease, *Quart. J. Med.*, 1921, **14**, 215.
3. Fishberg, A. M.: Anatomical Findings in Essential Hypertension, *Arch. Int. Med.*, 1925, **35**, 650.
4. Kernohan, J. W., Anderson, E. W., and Keith, N. M.: Arterioles in Cases of Hypertension, *Arch. Int. Med.*, 1929, **44**, 395.
5. Horine, E. F., and Weiss, M. M.: Hypertensive Heart Disease without Hypertension with Illustrative Case Reports, *Kentucky State Med. J.*, 1930, **28**, 464.
6. American Heart Association: Criteria for the Classification and Diagnosis of Heart Disease, New York, Paul B. Hoeber, Inc., 1928, p. 13.
7. Ophüls, William: Arteriosclerosis—Cardiovascular Disease: Their Relation to Infectious Diseases, Stanford Univ. Publication (Med. Sci. Series, vol. I, No. 1), Stanford University, 1921, p. 55.
8. Christian, Henry A.: Chronic Myocarditis—A Clinical Study, *J. Am. Med. Assn.*, 1918, **70**, 1009.
9. Ophüls, William: A Statistical Survey of Three Thousand Autopsies. Stanford University Publication (Med. Sci. Series, Vol. I, No. 3), Stanford University, 1926, p. 242.
10. Cabot, Richard C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 419.
11. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension: Study of 420 Cases, *Arch. Path.*, 1928, **5**, 930.
12. O'Hare, James P., and Walker, W. J.: Arteriosclerosis and Hypertension, *Arch. Int. Med.*, 1924, **33**, 343.
13. Master, Arthur M.: Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, *Am. Heart J.*, 1930, **5**, 291.
14. O'Hare, J. P., Calhoun, A. W., and Altnow, H. O.: Etiology of Chronic Myocarditis, *J. Am. Med. Assn.*, 1928, **90**, 1436.
15. Barker, N. W., Keith, N. M., and Kernohan, J. W.: Arterioles in Hypertensive Disease, Proceedings of the Staff Meetings of the Mayo Clinic, 1931, **6**, 172.

COMBINED TAPE-MEASURE AND STETHOSCOPE TUBE.

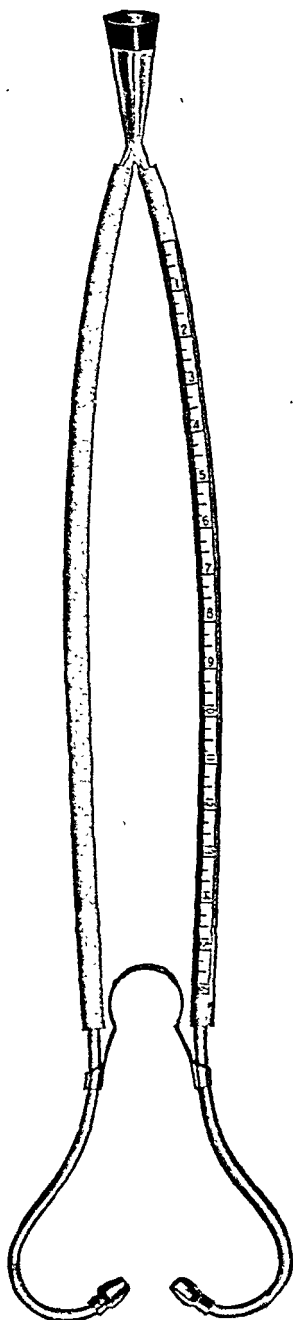
BY ARTHUR S. W. TOUROFF, B.S., M.D.,

ADJUNCT ATTENDING SURGEON, MT. SINAI HOSPITAL, NEW YORK CITY.

(From the Surgical Service of Dr. Harold Neuhof, Mt. Sinai Hospital, New York City.)

A SHORT flexible tape-measure is a necessary item in the armamentarium of the physician who attempts to achieve accuracy and precision in the field of physical diagnosis. Because of the frequency

with which such an instrument is forgotten, mislaid or lost, the average physician usually relies on his ability correctly to gauge



The tubing is manufactured by the Orsell Company, 108 West 78th Street, New York City.

certain measurements during the course of his examination of patients. Others, however, have attempted to obviate the difficulty by combining a readily available measuring tape with the stethoscope. This has been done by calibrating one of the rubber tubes of the stethoscope with ink, or by cutting notches in the rubber at measured intervals, with not entirely satisfactory results from the standpoint either of accuracy or durability of the markings.

Some time ago, while interested in the development of calibrated surgical drainage material, the idea of using the same method to calibrate stethoscope tubes occurred to us. An immediate trial convinced us of its value but disclosed one serious objection, namely, the inadvertent stretching of the tubing by the examiner while taking measurements. This objection was, however, readily overcome by a method of construction which we shall describe later.

The tubing is constructed in the following manner: Calibrations, 0.5 cm. apart, are vulcanized directly on a very thin strip of white rubber, 4 mm. wide, which constitutes the background. This calibrated rubber strip, in turn, is vulcanized and processed directly to the rubber tubing. The entire unit is then coated with a very thin layer of rubber, which imparts to it a smooth finish. Thus the calibrations which are now an integral part of the tubing are of permanent character and do not fade when subjected to hard usage, boiling, or chemical sterilization. Stretching of the tubing is prevented by incorporating several strong linen threads within its substance at the time of manufacture. This in no way interferes with its flexibility but merely prevents it from stretching. The calibrated strip begins at a point about 3 cm. from the distal end of the tube so that the portion immediately adjacent to the bell of the stethoscope is blank and enables one to hold the end of the tube without obscuring the calibrations.

We have found this simple device to be entirely adequate in accurately measuring the distances from the right and left cardiac borders to the sternum, the width of mediastinal dullness, the circumferences of various parts, etc. Undoubtedly other practical applications will suggest themselves.

THE CHANGES PRODUCED IN THE BLOOD PICTURE BY REMOVAL OF THE NORMAL MAMMALIAN SPLEEN.*

By E. B. KRUMBHAAR, M.D., PH.D.,

PROFESSOR OF PATHOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

THE effects on the blood picture of removal of the normal spleen have remained a subject of dispute in spite of the apparently simple nature of the problem and of the many studies that have been made upon it over more than a half century. While, for instance, the

* This article is also to appear in the Libman Memorial Volume and in *Le Sang* in a French translation.

majority believes that the spleen, in addition to its blood destroying function, has a stimulating effect on red blood cell formation (as evidenced by the anemia that follows its removal); others, chiefly German writers, have actively supported the view that the spleen normally inhibits red blood cell formation.

Difficulties Involved in This Problem. Though the reasons for this discord are not entirely clear, certain factors undoubtedly contribute, which have rarely received adequate consideration. In the first place the spleen, though accepted as an important member of the hemolytopoietic system, is one of the most variable of the viscera in size and weight in relation to general body weight, both at different stages of the individual's existence, and in different individuals of the same species, and in different species. In rabbits, for instance, it averages about 0.05 per cent of the body weight whereas in man, dogs and monkeys this ratio is more in the neighborhood of 0.25 per cent. It is therefore obvious that removal of the rabbit's spleen can hardly be expected to give as characteristic a light on the absent function as in the other cases; and yet negative results on this animal (a notoriously unsatisfactory subject for hematological investigations anyhow) have frequently served to cloud this issue. In Wade Brown's¹ studies on constitutional variation and susceptibility to disease, the spleen proved to be one of the most variable of the organs, and its gradual shrinkage with increasing age is a well-known occurrence. Study of splenic function has always been hampered by the double fact that, first, as a ductless organ, its action must usually be studied in a negative way, by the changes brought about by its removal, and yet, second, the effects of this removal, only eliminating one member of the reticulo-endothelial system, are soon masked by the compensating effects of other members of the system, especially bone marrow, liver and lymph nodes. While the changes following removal are more easily demonstrable on the hemolytic side (phagocytosis, hemosiderin, etc.), the hemopoietic shifts after splenectomy—especially those of a regulatory nature—are more difficult to determine. Even with such cytological evidence as the bone marrow hyperplasia that eventually follows splenectomy, it is difficult to evaluate how much of this is a true increase of hemopoietic tissue and how much is connected with the newly increased function of blood cell destruction. An extreme example of this type of difficulty is found in studies of splenectomy in lower orders. For instance, in the salamander the spleen is the chief organ of erythrocytopoiesis (Jordan and Speidel²); and yet after its removal new erythrocytes apparently can be differentiated in the general circulation as well as in the heart and liver sinuses.

Another source of confusion has been the tendency—so often present in biologic investigations—to base conclusions on too small a series of animals or on subjects studied over too short a period.

Where the change sought for is sure not to be marked, as is obvious from the long-continued disagreement, a large number of test subjects obviously becomes the more necessary. An adequate period of observation is necessitated not only to get past the ordinary effects of anesthesia and a major surgical operation, but also because the characteristic spleen effects are not best observed for a few weeks and not concluded until often many weeks after removal of the organ. And yet some of the experimental studies which led toward the use of splenectomy in pernicious anemia some 20 years ago, for instance, were limited to only two or three animals observed for 1 or 2 weeks after splenectomy. For similar reasons, the most careful controls are especially necessary. The importance of such details as use of the same instruments by the same person under identical conditions at the same time of day, reduction of technical error and emotional excitement in the test animals to a minimum, adequate pre-operative examinations and preparations to establish a true base line, has only been appreciated by us after years of acquaintance with the problem and, as might be expected, is often missed in the published reports. Not only are the normal variations in hemoglobin and red cell counts far greater than was earlier appreciated (*cp.*, L. Pearce's³ Study of the Blood Cytology of the Rabbit) but also seasonal variations (Platt and Freeman⁴) and emotion (Lamson,⁵ and Cannon and Izquierdo⁶) are known to play a not inconsiderable part.

Still further confusion has been caused by using the changes found after therapeutic removal of a pathological spleen in various anemias as throwing light on the relation of the normal spleen to blood formation and destruction. Not only is this *ipso facto* a faulty procedure in general, but also in the case of the spleen, the diseased organ is known often to be a site of greatly increased blood destruction. Removal of a diseased organ, therefore, would tend on general grounds to lessen an anemia, and also in this case the removal of a hyperactive blood destroying factor would raise the blood level, irrespective of the normal organ's effect on blood formation. Thus two of the chief supports for the view that the spleen has an inhibiting effect on red blood cell formation can be shown to be vulnerable to destructive criticism.

Legitimate differences in interpretation also play their rôle. Thus recently Chiatellino and Goldberger⁷ report that three splenectomized dogs showed a much greater rise of hemoglobin and erythrocytes when taken to high altitudes than did 3 controls, on account of the absence of the so-called inhibitory effect of the spleen. The protocols, however, show that the splenectomized dogs started anemic (4.9, 5.0 and 4.7 million reds *vs.* 8.0, 7.3, 5.4 respectively of the controls) and therefore had a greater demand for an erythrocytic increase. One is naturally curious also to know why the splenectomized animals were anemic before being taken to high altitudes! The data of other (*e. g.*, Roese⁸) are so inadequately presented that deductions are difficult.

TABLE 1.—THE LITERATURE ON THE ERYTHROCYTE COUNT AFTER SPLENECTOMY.
For Appearance of Anemia.

Bathias ¹² : (rabbits for 2 to 4 weeks).	Sorge ⁵⁴ : (mice and rats, drop up to 60 per cent, slight polyglobulia in 3 weeks).
Bittner ¹³ : (rabbits, slight, inconstant).	Stachelin ⁵⁵ : (man).
Bizzozero and Salvatelli ¹⁴ : (g. pigs, dogs).	Swain ⁵⁶ : (man).
Bucalossi ¹⁵ : (reference not available).	Takagi ⁵⁷ : (dogs).
Catellani ¹⁶ : (man).	Tauber ⁵⁸ : (15 different animals).
Darling ¹⁷ : (man).	Troilo ⁵⁹ : (g. pigs, months).
Eddy ¹⁸	Viale ⁶⁰ : (reference not available).
Emilianow ¹⁹ : (dogs).	Vulpus ⁶¹ : (goats and rabbits for 1 month).
Fowler ²⁰ : (man).	Warthin ⁶² : (sheep, goats).
Freyling ²¹ : (rabbits, slight, 2 weeks).	Weickel and Gebhardt ⁶³ : (dogs, quick anemia and no quick rise; dogs back to normal in year).
Gibson ²² : (dogs, maximum 60th day).	Winogradow ⁶⁴ : (dogs, drop followed by hyperplasia in 150 to 200 days).
Godard and Palosi ²³ : (g. pigs, normal in 4 to 6 weeks).	Wlaef ⁶⁵ : (man, splenectomy for cyst, maximum drop on 25th day; normal in 6 months).
Grigorescu ²⁴ : (man and dogs).	Zesius ⁶⁶ : (man and various animals).
Hartmann and Vaquez ²⁵ : (several human cases).	
Hirschfeld and Fabisch ²⁶ : (16 rabbits, drop then rise).	
Hitzrot ²⁷ : (man, majority of cases).	
Istomanowa, <i>et al.</i> ²⁸ : (dogs, confirm all our findings).	
Jepson ²⁹ : (man, drop of 1.7 mill. on first day).	
Johnstone ³⁰ : (dogs).	
Keller ³¹ : (g. pigs, slight for 10 days).	
Krumbhaar and Musser ³² : (monkeys, slight).	
Laudenbach ³³ : (dogs, 4 days to 4 mos.).	
Levi ³⁴ : (rabbits, 14 per cent).	
Loesch, <i>et al.</i> ³⁵ : (dogs).	
Maggiolini ³⁶	
Malassez and Picard ³⁷ : (3 dogs, Hb. even lower).	
Matthews and Miles ³⁸ : (man, long slight drop though authors conclude that reds behaved normally).	
McCoys ³⁹ : (man).	
Meyers ⁴⁰ : (boy).	
Moleu ⁴¹ : (rabbits, first marked drop, then overswing in 8 to 65 days).	
Moslere ⁴² : (dogs).	
Musser ⁴³ : (man, splenectomy for cyst, protracted drop).	
Musser and Krumbhaar ⁴⁴ : (dogs).	
Nicolas and Dumoulin ⁴⁵ : (dogs).	
Noguchie ⁴⁶ : (man).	
Ort ⁴⁷ : (rabbits, 60 days).	
Pugliese and Luzzati ⁴⁸	
Pugliese and Smyth ⁴⁹ : (man, still anemic 2 to 4 years later).	
Roughton, Legg and Emery ⁵⁰ : (man).	
Schindeler ⁵¹ : (reference not available).	
Schulze ⁵² : (man).	
Silvestri ⁵³ : (dogs).	

* In parentheses are found indications of the species involved and occasional details about the change.

Against Fall in Erythrocytes.

Asher and Du Bois⁶⁷: (3 rabbits, decrease very slight if associated with thyroid).

Asher and Sollberger⁶⁸: (rabbit, and short period. Slight if fed iron).

Asher and Vogel⁶⁹: (rise in dogs).

Azzurini and Massart⁷⁰: (4 dogs, 15 months; slight rise 1 to 3 days).

Bachman and Hultgren⁷¹: (rabbits, no details; only followed a few days).

Gabbi⁷²: (rabbits, neutral; g. pigs, rise).

Heaton⁷³: (man, no change).

Hirschfeld and Weinert⁷⁴: (man, rabbits).

Huygebart⁷⁵: (no change in dog).

Kreuter⁷⁶: (9 monkeys, show slight drop 9 weeks after).

Paton, *et al.*⁷⁷: (dog, cat, rabbit. "No change" but some showed our mild anemia).

Ponticcia⁷⁸: (rabbits, rise; reference not available).

Port⁷⁹: (rabbits, no change).

Pouchet⁸⁰: (dog, cat, bird, triton, fish; no change, no counts given).

Rosse⁸¹: (dogs and rabbits, short drop followed by rise, no pre-operative figures).

Schiff⁸²: (neutral and rise; reference not found).

Schwunert and Krzywanek⁸³: (dog, no drop while resting).

Shelley⁸⁴: (2 cases of trauma, first had no counts between the 18th and 180th days, the second showed a distinct anemism from the 3d to 12th month of observation; neither had counts before the injury).

Tizzoni and Filetti⁸⁵: (reference not available).

Zanda⁸⁶: (dog).

It is proposed now to examine the evidence concerning the effect of removal of the normal spleen, chiefly in dogs, rabbits, guinea-pigs and man, on the level of erythrocyte count, hemoglobin, reticulocyte percentage, fragility of erythrocytes and blood platelet count. On account of the infectious anemia (Bartonella) lit up by splenectomy in rats (Lauda⁹) this animal is not included, though evidence points toward development of a transient anemia even in rats free of this infection. The leukocyte changes (enduring leukocytosis with tardy lymphocytosis and eosinophilia) have been sufficiently discussed elsewhere.

The Effect of Splenectomy on the Erythrocyte Count. The point that has received the most attention, at first glance one of the simplest yet provoking the most contradiction, is the level of the erythrocyte and hemoglobin counts. As the reports are too numerous to be considered *seriatim*, the accompanying table of reported changes in the erythrocyte count has been prepared, though it is obvious that many minor variations are thus necessarily omitted. As the hemoglobin change is generally recognized as not significantly different, it can well be omitted; its consideration is also complicated by the exchange with muscle hemoglobin (Whipple, *et al.*¹⁰) and Ray's¹¹ observation that after splenectomy, the oxygen capacity of the erythrocytes decreased more rapidly than did the pigment, *i. e.*, that a nonfunctioning hemoglobin had also to be taken into account.

From Table 1 it is seen that the majority of investigations has found a significant anemia developing after splenectomy, but that a not inconsiderable number has found either no significant change or an actual rise of erythrocytes. Most of those finding an anemia have, like ourselves, found it beginning to develop shortly after operation, reaching a maximum in a few weeks and disappearing after several more. Hirschfeld,⁸⁶ however, who earlier²⁶ failed to find any anemia, has recently reported an initial, short anemia in experimental animals followed by polyglobulia at a time when others found the anemia developing or near its maximum. Roese,⁸ of the same school of thought, reported similar changes—the explanation being that the early drop is connected with the loss of the spleen's iron-regulatory function, while the later rise is due to the loss of the spleen's inhibitory influence on bone-marrow hemato-poiesis. Some of those finding the slower developing anemia, have found a polyglobulia (*e. g.*, Winogradow,⁶⁴ and occasionally ourselves), for which an overcompensatory mechanism has been suggested as a possibility, but where unassociated chance changes in general condition cannot be definitely ruled out. Where no anemia has been found, the spleen was thought to be indifferent toward blood formation; the suggestion has been made by those finding an anemia that possibly accessory spleens have been overlooked at operation in such cases, though in the later reports this item has usually been covered. It is but fair to add, too, that many of the articles

reporting anemia are from an early period when the precautions I have previously referred to were least followed; and while many—perhaps most—of those failing to find a postsplenectomy anemia should be similarly discounted, there are a few that remain difficult to reconcile. The studies of Azzurini and Massart,⁷⁰ for instance, though on a small number of dogs, bear intrinsic evidence of such thoroughness that it is impossible for the advocates of postsplenectomy anemia to disregard them. The mild anemia of some of our own dogs, too, suggest that the spleen's influence is not of such intensity that its absence is *always* clearly manifested by present methods.

Our own studies, which have now continued at intervals over 21 years, have accumulated evidence on 32 dogs and 6 monkeys, sufficiently uncomplicated by other experiments such as bleeding, administration of oleate, hemolytic serum, etc., to throw light on the effect of absence of the spleen *per se*. All have shown anemia, the red blood cell count dropping on an average of 1.49 million cells per c.mm. (extremes 0.5 to 3.5 million) with similar falls in hemoglobin. Occasional blood-volume studies tend to show that this is a true diminution in number and not a change in concentration. Not only is the drop much more variable than in the first series reported by us, but the time of onset and duration have, as would be expected, shown considerably more variation. In the whole series, anemia was found to extend from the first to the 70th day after splenectomy (extremes) and reached its maximum, on the average, on the 29th day. (Extremes of maximum anemia fell between the 5th and 60th days.) The intact control dogs examined over long periods showed hardly more than the variations of the method's error (3 to 4 hundred thousand), if kept in good condition free from infection. The fact that these are less than the "normal" variations above referred to tends to show that observance of strictly standard conditions, especially the successful avoidance of emotional changes, minimizes normal variation. The controls on which such operations as partial hysterectomy, omentectomy, lymphadenectomy and unilateral nephrectomy were performed, sometimes showed an anemia comparable to the milder splenectomy anemias, but it reached its maximum at a significantly earlier point (2 to 14 days) and made a quicker recovery. While requiring consideration, therefore, it seems proper to regard these as nonspecific reactions separable from true splenic effects. In our monkeys, on the other hand, the slighter anemia reached its maximum on the 9th day after splenectomy and it might well be that other animals would reach a maximum still earlier. Not only must general species differences here be taken into account, but also the shorter natural duration of life in the smaller laboratory animals. It is worth noting that in Table 1 Kreuter,⁷⁶ the only other observer of the postsplenectomy blood changes in monkeys, is listed on his own interpretations as against

the development of anemia, though analysis of his figures showed a slight anemia that was very little less than that observed by us.

In recent years we have paid especial attention to the immediate postoperative changes in the blood pictures on account of the transient rise reported by some observers at this time. In 17 of our dogs such a rise was found (0.2 to 1.2 million cells per c.mm.) lasting from 1 to 3 days; but similar rises were also found in most of the controls. Attempts to evaluate by blood volume studies the factor of postoperative anhydremia in this change have thus far not given consistent results, but are still being continued. Loesch, Witts and Zimmermann³⁵ state that the severity of the anemia is masked by an oligemia, as shown by their blood volume determinations, and that the total amount of circulating hemoglobin may be reduced to one-third. It was also hoped that study of the reticulocyte* percentage as a sign of erythropoietic activity might throw light on the nature of this frequently observed rise. Six of 8 recently splenectomized dogs showed a rise in the reticulocyte percentage from a preoperative average of 0.3 per cent to 1.2 per cent 1 and 2 days after operation—slight, to be sure, as compared with the high values obtained in disease, but large when compared to our experience with normal dogs. Of 6 controls, 3 intact animals varied between 0.01 and 0.3 per cent reticulocytes (*i. e.*, normal) over considerable periods up to 19 months, while 2 undergoing unilateral nephrectomy showed no operative rise. While such evidence is based on far too few animals to be conclusive, and while it is impossible to rule out nonspecific postoperative effects, nevertheless it tends to indicate that splenectomy has a tendency in the dog to be followed for a few days by an increased number of reticulocytes in the peripheral blood. In the monkey Krumbhaar and Musser³² failed to find any signs of regeneration in the peripheral blood, either of blasts or reticulocytes, which were actually diminished. Whether such an increase indicates increased bone marrow activity with an overflow into the blood or whether it is a sign of decreased maturing ability of the bone marrow with consequent delivery of immature cells to the blood stream is a matter requiring further investigation. Just as in the liver treatment of pernicious anemia the beneficent effect is shown first by an increase of reticulocytes (relatively more mature than the megaloblasts) and next by an increase of the still more mature normocytes, so here the converse is possible, that the increase in reticulocytes (if not accompanied by a true increase in the total number of erythrocytes) might be looked upon as a sign of interference with their normal maturation rather than of true increased erythropoiesis.

The Effect of Splenectomy on the "Fragility" of Erythrocytes. This is one of the few phases of this problem in which there is sub-

* This term, proposed by me (J. Lab. and Clin. Med., 1922-1923, 8, 11) to indicate those immature erythrocytes which exhibit a reticulum after vital staining, should not be confused with the reticular cells of the reticuloendothelial system.

stantial unanimity. Whether the spleen is removed from normal animals or therapeutically in disease, there is always an increase of the resistance of erythrocytes to hypotonic salt solution, as well as to most other forms of damage. This has proved of clinical importance in hemolytic jaundice, where splenectomy brings the fragile cells to a point nearer normal resistance. This fact, coupled with observations that blood cells emerging from the spleen appear to be less resistant than the entering blood cells, indicates that the spleen has a hemocatatonic (weakening) effect on certain (probably the effete) erythrocytes (Bottazzi⁸⁷). While the great majority of investigators has found such an increase (we, for instance, having found it constantly in man, monkey and dog), only four investigators (as Lauda⁹ points out in his review) have had contrary results. Frenckell and Nekludon,⁸⁸ who have found a constant hypercholesterolemia after splenectomy in dogs, cats and rats, think this to be the cause of the increased resistance.

Immature Erythrocytes in the Circulation after Splenectomy. A number of investigators have reported showers of Jolly bodies, or more rarely of nucleated forms, appearing in the circulation in man (Morris,⁸⁹ Hirschfeld and Weinert,⁷⁴ Muehlbradt⁹⁰ and many others) which sometimes persist over long periods. Similar findings have been reported in animals (mice, Lauda and Haam;⁹¹ rats, Waltz;⁹² rabbits, Karlbaum,⁹³ Ponticaccia;⁷⁸ guinea pigs, Keller;³¹ dogs, Loesch, Witts and Zimmermann,³⁵ Karlbaum,⁹³ Takagi,⁵⁷ Weicksel and Gebhardt,⁶³ etc.). This we have never been able to substantiate, even during the period of anemia, though we have returned to the search on numerous occasions and repeatedly on the stained spreads taken at appropriate times. Beyond the occasional normoblast found even in normal dogs' blood, we have not been able to find any nucleated forms on Jolly bodies at any time after splenectomy. Istomanowa, Wjassinkow and Swjatskaja²⁸ likewise failed to find any "granular crises." Such discrepancies can only be recorded here in the hope that a satisfactory explanation will eventually be forthcoming.

Reticulocytes. The behavior of the reticulocytes immediately after operation has already been discussed. In our experience with dogs from 10 to 42 days after splenectomy (*i. e.*, coincident with the maximum amount of anemia), the reticulocyte would again rise (0.4 to 1.0 per cent), sometimes to stay increased during the period of observation of more than a year (like the bone marrow hyperplasia that we have elsewhere reported). The monkeys, however, never showed any increase, probably on account of the mildness of the anemia. Mole⁴¹ in rabbits and Benhamou and Nouchy⁹⁴ only found a transient postoperative reticulocytosis, like that found in the majority of our dogs (as previously noted). We would again emphasize that while reticulocytosis undoubtedly indicates an alteration in erythropoiesis, and possibly a sign of increased erythro-

poietic activity, it is not necessarily and always a sign of such a change. As Witts⁹⁵ points out in his recent Goulstonian lectures, "Estimations of the number of reticulocytes have added much to our knowledge of the rate of blood formation in disease, but this test must not be used uncritically, and it needs collateral support. Reticulocytes appear in the blood stream when the marrow is irritated by a variety of substances, such as shellac and colchicin, and marrow irritation must be distinguished from a real increase of red cell production. I have seen reticulocyte counts of 6 per cent in aplastic anemia, though the absolute number was small, and this is not surprising when we remember that a few remnants of hyperplastic marrow are usually left in this disease. An increased delivery of red cells into the circulation may be unaccompanied by a rise in the number of reticulocytes, as when a transfusion is given at the beginning of liver treatment in pernicious anemia." We have already referred to the possibility of a disturbance of normal maturation being the responsible factor.

The Nature of the Anemia. In explanation of the nature of the postsplenectomy anemia, its occurrence is obviously due to the loss of something contained in the spleen. Asher and his school have reported an increased loss of iron after splenectomy, which would afford a satisfactory solution as the anemia is apparently one of decreased blood formation. Not only have their published protocols seemed inadequate to clinch the point, however, but they have not been sufficiently confirmed by others. Our earlier studies on this point having been inconclusive ("The Spleen and Anemia," p. 112 *et seq.*), we have recently returned to this problem with better methods, more animals and varied controls; though the results were not as striking as one might wish, we believe that they confirm Asher's view that there is an increased loss of iron after splenectomy (unpublished studies). We have not been able to prevent the anemia by high iron diets. The situation remains then, as previously stated, that in the light of the evidence at hand, including the stimulating action of splenic extracts (Danilewski,⁹⁶ Leake,⁹⁷ ourselves and others), the loss of the spleen is thought to produce anemia, not by the loss of a center of blood formation (though this may contribute in some cases) but by the loss of a stimulant to the bone marrow or of one of its purveyors of building material, especially iron. As Lauda⁹ points out, analogous to the action of lowered body temperatures in stimulating the heat-producing centers in the medulla, and to the stimulation of respiration by accumulated CO₂ in the blood, so products of erythrocytes destroyed in the spleen may perhaps stimulate blood-cell formation, which stimulus would temporarily be diminished in the absence of the spleen until the process was fully taken over by other members of the reticuloendothelial system. Such increased postsplenectomy activity in liver, lymph nodes and bone marrow has been repeatedly demonstrated (See "The Spleen

and Anemia," pp. 164, 201) and is, I believe, generally accepted. With such a dual action of the spleen in opposing directions (lowering the erythrocyte count by doing away with cells and helping to raise it by stimulating erythropoiesis), it is easier to comprehend the varying results that have so long complicated this problem. Such an explanation, too, is in accord with our findings (since confirmed by others) that the anemia that follows a hemolytic agent, while producing a smaller drop in the splenectomized dog, requires a longer period of repair. It does not produce as great a drop because if anemic, there is less distance to go, also because the cells are more resistant, and one of the agents for removing erythrocytes is absent; but it lasts longer because a stimulant to the bone marrow is absent.

The anemia once established, the increased resistance of the erythrocytes may be regarded as the usual sequel of anemia, while its eventual disappearance is adequately explained by the compensatory bone marrow hyperplasia. The persistence of this hyperplasia may be due, as Johnstone³⁰ states, to the general law of regeneration in excess; but an added factor for consideration is the cellular increase brought about by the assumption of the absent spleen's hemolytic function.

The Effect of Splenectomy on the Blood Platelet Count.—Kaznelson's⁹⁸ demonstration in 1916 that splenectomy had a remarkably beneficial effect on those cases of purpura that had been shown by Frank⁹⁹ (1915) to have a low blood platelet count has stimulated considerable interest in this phase of the spleen problem. The rise in the platelet count has been found by all observers both experimentally and clinically, though the evidence varies as to the duration and cause of the increase. Experimentally, for instance, it has been found in dogs by Weicksel and Gebhardt,⁶³ Binet and Kaplan,¹⁰⁰ Loesch, *et al.*,³⁵ Steiner and Gunn,¹⁰¹ and clinically, by Bachman and Hultgren,⁷¹ Benhamou and Nouchy,⁹⁴ Dawbarn, *et al.*,¹⁰² Galloway,¹⁰³ Holloway and Blackford,¹⁰⁴ Leotta,¹⁰⁵ Litchfield,¹⁰⁶ Quenu and Stoianovitch,¹⁰⁷ Rivoire,¹⁰⁸ and many others. (See also 30 cases reviewed by Leschke and Wittkower,¹⁰⁹ and 101 cases by Spence¹¹⁰.)

The findings as to the duration of the rise have not been so uniform. In our dogs, the count was from 50 to 200 per cent higher at the end of observation (3 to 12 months) than before operation. Immediately following the operation there was a considerable rise (like that of the "operated" controls) but after a drop toward normal a second rise was observed which was lasting. While others have found this lasting rise (Liles,¹¹¹ experimentally, Galloway¹⁰³ and in a number of the reports collected by Leschke and Wittkower,¹⁰⁹ and Spence¹¹⁰) many others, including 3 of Kaznelson's⁹⁸ original cases, have returned to normal (in the experimental observations) or to pathologically low limits (in the cases of thrombopenic purpura), sometimes with and sometimes without return of hemorrhagic symptoms. Such variations have led Steiner and Gunn,¹⁰¹ on the basis of control operations to splenectomy on rabbits, to conclude

that the thrombocytosis of the latter operation does not differ from the others in time of occurrence, degree or duration. They did not, however, in my opinion follow their test animals for a sufficiently long period to invalid to the majority view that the postsplenectomy thrombocytosis is of considerably longer duration and degree than simple postoperative thrombocytosis. The same increased fluctuation of successive counts ("irritability of the blood picture") after splenectomy has been noted for the blood platelets as for the erythrocyte and hemoglobin determinations (Loesch, Witts and Zimmermann,³⁵ Sorge,⁵⁴ our own observations, and others).

As to the cause of the changes in the platelet count after splenectomy in disease, Frank⁹⁹ based the thrombopenia on a deficient formation in the bone marrow, which was then stimulated by removal of the spleen, while Kaznelson⁹⁸ believed there was an increased destruction of the platelets in the spleen. Counts of the platelets in the blood entering and leaving the spleen have not decided the matter, though on the whole this evidence favors the thrombolytic action of the spleen, as does the histologic evidence of hyperplasia of phagocytic cells in the spleen in the purpura cases and the suddenness of the rise of the platelet count after splenectomy. The long duration of the experimental thrombocytosis, on the other hand, points either toward the lasting loss of an inhibiting action on platelet formation in the bone marrow or to inadequacy on the part of other members of the reticuloendothelial system to take over the lytic function for platelets; as the system is able to do for erythrocytes. Until decisive evidence is available, it would be reasonable to assume that the postsplenectomy thrombocytosis may be the result of both decreased thrombolysis and decreased inhibition of platelet formation.

Summary. While definite conclusions are obviously impossible on many of these matters, the following statements can be said to have the support of the more weighty evidence.

In the normal mammal, splenectomy causes a true, mild temporary anemia that varies both in individuals and in species and in time of appearance, degree and duration. This is accompanied by an increase in the reticulocyte count, an increase in the resistance of the erythrocytes, both of which are apparently responses to the anemia. This anemia is due to a loss with the spleen of a property which aids erythrocyte formation, such as the conservation of the iron of breakdown erythrocytes. This function is eventually taken over, at least in large part, by other members of the reticuloendothelial system. The normal spleen does not have an inhibitory action on erythropoiesis in the bone marrow.

The reason for the appearance of Jolly bodies and nucleated forms which has been reported by the majority of investigators, has not been explained. It is possible that they represent a loss with the spleen of a property of maturing erythrocytes, rather than the loss of a brake on erythropoiesis.

The cellular hyperplasia in the bone marrow observed after splenectomy represents not only the compensatory response to the anemia but also the loss of an important organ concerned with hemolysis, *i.e.*, many of these hyperplastic cells are functioning on the hemolytic side of the hemolytopoietic system.

Splenectomy both in normal animals and in cases of thrombopenic purpura causes a marked rise in the platelet count, which is more persistent than other postoperative thrombocytoses. It has not yet been settled whether this is due to the removal of a platelet death-house or of an organ that tends to inhibit platelet formation or to both.

REFERENCES.

1. Brown, Wade: Harvey Lectures, 1928-1929, Baltimore, Williams & Wilkins Company.
2. Jordan, H. E., and Speidel, C. C.: *Am. J. Anat.*, 1930, 46, 55.
3. Pearce, L.: *J. Exp. Med.*, 1930, 51, 83.
4. Platt, V. E., and Freeman, R. G.: *Proc. Soc. Exp. Biol. and Med.*, 1930, 27, 687.
5. Lamson, P. D.: *J. Phar. and Exp. Ther.*, 1915, 7, 189.
6. Cannon, W. B., and Izquierdo, J. J.: *Am. J. Physiol.*, 1928, 84, 545.
7. Chiatellino, A., and Goldberger, S.: *Arch. per le sci. med.*, 1930, 15, 407.
8. Roese, G.: *Zts. klin. Med.*, 1925, 102, 454.
9. Lauda, E.: *Ergeb. d. inn. Med. u. Kinderheilk.*, 1928, 34, 1; *Klin. Wchnschr.*, 1925, 4, 1587.
10. Whipple, C. H., *et al.*: *Am. J. Physiol.*, 1926, 76, 693; *J. Exp. Med.*, 1932, 55, 637.
11. Ray, C. R.: *Am. J. Physiol.*, 1928, 86, 138.
12. Bathias: *Thèse*, Lyon, 1903 (quoted by Nicolas and Dumoulin).
13. Dittner, A.: *Fol. Hematol.*, 1913, 15, 237.
14. Bizzozero, C., and Salvioni, C.: *Arch. par le sci. med.*, 1881, 4, 53.
15. Bucalossi: *Cong. Soc. Ital. di Chirurg.*, October, 1908 (Abstract *Fol. Hematol.*, 1909, 7, 133).
16. Catellani, S.: *Gaz. d. ospedali*, 1897, 18, 75.
17. Darling, C. C.: *Med. Rec.*, 1911, 79, 110.
18. Eddy, N. B.: *Endocrinol.*, 1921, 5, 461.
19. Emilianow: *Arch. des sciences de biol. de St. Petersburg*, 1893, 2, 135.
20. Fowler, R. S.: *J. Am. Med. Assn.*, 1914, 64, 198.
21. Freytag: *Pfuger's Arch.*, 1907, 120, 517.
22. Gibson, J. L.: *J. Anat. and Physiol.*, 1885-86, 20, 100; 324, 456.
23. Godard, H., and Palios, C.: *Comp. rend. Soc. de biol.*, 1929, 101, 775.
24. Grigorescu: *Arch. de Physiol.*, 1891, Series 5, 3, 561.
25. Hartmann and Vaquez: *Comp. rend. Soc. de biol.*, 1897, 4, 126.
26. Hirschfeld, H., and Fabisch, W.: *Fol. Hematol.*, 1928, 37, 262.
27. Hitzrot, J. M.: *Ann. Surg.*, 1918, 67, 540.
28. Istomanowa, T., Mjassnikow, A., and Swjatskaja, A.: *Ztz. f. d. ges. exp. med.*, 1926, 52, 160.
29. Jopson, W.: *J. Am. Med. Assn.*, 1905, 45, 690.
30. Johnstone, R. M.: *Arch. Surg.*, 1922, 5, 159.
31. Keller, E.: *Fol. Hematol.*, 1931, 44, 413.
32. Krumbhaar, E. B., and Musser, J.: *Arch. Int. Med.*, 1923, 31, 686.
33. Laudenbach, J.: *Arch. d. Physiol. norm. et path.*, 1897, Series 5, 9, 385.
34. Levi, M.: *Patologica*, 1929, 21, 126.
35. Loesch, J., Witts, L. F., and Zimmermann, A.: *J. Metabol. Res.*, 1924, 6, 297.
36. Maggioriani: (In Krause *Anat. des Menschen*. Quoted by Hirschfeld and Fabisch).
37. Malassez and Picard: *Gaz. m'ed. de Paris*, 1878, 7, 317.
38. Matthews, E., and Miles, A.: *Edinb. Med. J.*, 1907, 64, 294.
39. McCoy, J. C.: *Ann. Surg.*, 1911, 54, 597.
40. Meyers, J.: *J. Am. Med. Assn.*, 1909, 52, 1231.

41. Mole, R. H.: *J. Path. and Bact.*, 1925, **28**, 637.
42. Mosler: *Path. u. Ther. d. Leuk.*, 1872, Berlin, p. 40.
43. Musser, J.: *Am. J. Med. Sci.*, 1911, **142**, 501.
44. Musser, J., and Krumbhaar, E. B.: *J. Exp. Med.*, 1913, **18**, 487.
45. Nicolas, J., and Dumoulin, L. E. and F.: *J. de Phys. et Path.*, 1903, **5** (5), 818.
46. Noguchi, Y.: *Berl. Klin. Wehnschr.*, 1912, **49**, 1839.
47. Orr, T. G.: *J. Lab. and Clin. Med.*, 1916-17, **2**, 895.
48. Pfeiffer, D., and Smyth, C.: *Ann. Surg.*, 1924, **80**, 562.
49. Pugliese, A., and Luzzatti, T.: *Arch. p. le sci. med.*, 1900, **24**, 1;
50. Houghton, E. W., Legg, T. P., and Emery, W. d'E.: *Lancet*, 1907, **1**, 1696.
51. Schindeler: *Beitr. z. Kenntn. d. Veränd. des Their. Organismus*. Dissertation, Creifswals, 1870 (not available).
52. Schulze, F.: *Beitr. z. klin. Chir.*, 1911, **74**, 456.
53. Silvestri: *Patologica*, 1913, **5**, 145.
54. Sorge, G.: *Boll. Soc. Biol. Sper.*, 1926, **1**, 443.
55. Staehelin: *Deut. Arch. klin. Med.*, 1903, **76**, 364.
56. Swain, J.: *Bristol Med. J.*, 1910, **28**, 223.
57. Takagi, T.: *Fol. Hematol.*, 1923, *Arch.*, **28**, 95.
58. Tauber, A.: *Virchow's Arch. f. path. Anat.*, 1889, **96**, 29.
59. Troilo, E. B.: *Rev. Sud Americ. de Endocrinol.*, 1928, **11**, 554; *Arch de cardiol. y. hematol.*, 1929, **10**, 10.
60. Viale, G.: *Riv. di patologia sperim.*, 1928, **3**, 450.
61. Vulpius, C.: *Beitr. z. klin. Chir.*, 1894, **11**, 633.
62. Warthin, A. S.: *J. Med. Res.*, 1902, **2**, 435.
63. Weicksel, G., and Gebhardt: *Zts. f. d. ges. Exp. Med.*, 1924, **43**, 659; 1926, **50**, 415.
64. Winogradow, K.: *Centralbl. f. d. med. Wissenach.*, 1882, **20**, 900.
65. Wlaeff: *Comp. rend. Soc. biol.*, 1903, **54**, 1221.
66. Zesas, D. G.: *Arch. f. klin. Chir.*, 1883, **28**, 157, 815.
67. Asher, L., and Du Bois: *Biochem. Zts.*, 1917, **82**, 41.
68. Asher, L., and Sollberger, H.: *Biochem. Zts.*, 1913, **4**, 13.
69. Asher, L., and Vogel, H.: *Biochem. Zts.*, 1909, **17**, 297.
70. Azzurini, F., and Massart, S.: *Speriment.*, 1904, **58**, 629.
71. Bachman, E. L., and Hultgren, C.: *Comp. rend. Soc. biol.*, 1926, **94**, 942.
72. Gabbi: *Beitr. z. path. Anat.*, 1896, **19**, 647.
73. Heaton, G.: *Brit. Med. J.*, 1899, **2**, 476.
74. Hirschfeld, H., and Weinert, A.: *Ber. Klin. Wehnschr.*, 1914, **51**, 1013, 1026.
75. Huygebaert, E.: *Arch. Internat. de Pharmacody. et de Ther.*, 1924, **29**, 435.
76. Kreuter: *Arch. f. klin. Chir.*, 1914-15, **106**, 191.
77. Paton, N., Culland, C. L., and Fowler, J. S.: *J. Physiol.*, 1902, **28**, 83.
78. Ponticaccio: *Gior. d. clin. med.*, 1925, **6**, 2. (Reference not available.)
79. Port, F.: *Arch. f. exp. Path. u. Phar.*, 1912, **72**, 307; 1913, **73**, 251.
80. Pouchet: *Gaz. méd. Paris*, 1878, **7**, 316.
81. Schiff, M.: *Die Verrichtungen der Milz*. (Reference not found.)
82. Schwunert, A., and Krzywanek, F. W.: *Pfuger's Arch. f. d. ges. Physiol.*, 1926, **215**, 187.
83. Shelley, H. J.: *Ann. Surg.*, 1931, **93**, 1064.
84. Tizzoni, G., and Fileti: *Atti. d. real. Acad. d. Lincei*, quoted by Hirschfeld and Fabisch. (Reference not available.)
85. Zanda: *Sperimentale*, 1893, **47**, 14. *Mem. orig.*
86. Hirschfeld, H.: *Deut. Med. Wehnschr.*, 1915, **41**, 1120.
87. Bottazzi, P.: *Spermentale, Sez. biol.*, 1894, **48**, 433.
88. Freneckell, C., and Nekludon, V. N.: *Arch. f. d. ges. Physiol.*, 1928, **220**, 356.
89. Morris, R. S.: *Arch. Int. Med.*, 1915, **15**, 514.
90. Muchlbradt: *Deut. Zts. f. Chir.*, 1930, **228**, 365.
91. Lauda, E., and Raam, E.: *Zts. f. d. gen. Exp. Med.*, 1927, **58**, 322. See also *Proc. Soc. Exp. Biol. and Med.*, 1931, **29**, 260.
92. Waltz, W.: *Zts. f. d. ges. Exp. Med.*, 1923, **31**, 325.
93. Karlbaum: *Fol. Hematol.*, 1916, **20** (3), 215.
94. Benhamou, E., and Nouchy, A.: *Comp. rend. Soc. biol.*, 1932, **109**, 401.
95. Witts, L. J.: *Lancet*, 1932, **1**, 497.
96. Danilewski, B.: *Arch. f. d. ges. Physiol.*, 1895, **61**, 264.
97. Leake, C. D., and E. W.: *J. Phar. and Exp. Ther.*, 1923, **22**, 75, 109, 401; *Am. J. Men. Sci.*, 1924, **168**, 819.

98. Kaznelson, P.: *Wehnschr. klin. Med.*, 1916, No. 46, p. 1451. See also *Zts. klin. Med.*, 1919, 87, 133.
99. Frank, E.: *Berl. Klin. Wehnschr.*, 1915, 52, 454, 490.
100. Binet, L., and Kaplan, M.: *Comp. rend. Soc. biol.*, 1927, 97, 1128.
101. Steiner, P. E., and Gunn, F. D.: *Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 1088.
102. Dawbarn, R. Y., Earlam, F., and Evans, W. H.: *J. Path. and Bact.*, 1928, 31, 833.
103. Galloway, J. F.: *Lancet*, 1931, 2, 1235.
104. Holloway, J. K., and Blackford, L. M.: *Am. J. Med. Sci.*, 1924, 168, 723.
105. Leotta, N.: *Arch. e. att. soc. ital. d. chir.*, 1926, 32, 500.
106. Litchfield, H. R.: *Pediatric Bull.*, 1929, 1, 5.
107. Quenu, J., and Stoianovitch, S. M.: *Bull. et mém. d. l. Soc. nat. de chir.*, Paris, 1929, 55, 111.
108. Rivoire, R.: *Presse méd.*, 1930, 38, 358.
109. Leschke, E., and Wittkower, E.: *Zts. f. klin. Med.*, 1926, 102, 649.
110. Spence, A. W.: *Brit. J. Surg.*, 1927-28, 15, 466.
111. Liles, R. T.: *Proc. Soc. Exp. Med.*, 1925-26, 23, 489.

THE VAN DEN BERGH REACTION AND THE BROMSULPHALEIN TEST IN THE ESTIMATION OF HEPATIC FUNCTIONAL IMPAIRMENT.

BY A. CANTAROW, M.D.,

INSTRUCTOR IN MEDICINE, JEFFERSON MEDICAL COLLEGE.
PHILADELPHIA.

(From the Laboratory of Biochemistry, Jefferson Hospital and the Department of
Medicine, Jefferson Medical College, Philadelphia.)

NUMEROUS reports in recent years, embodying the results of extensive experience with the use of various methods for the determination of hepatic functional efficiency, almost invariably emphasize the fact that the excretory function of the liver is the only one which can be investigated clinically with any degree of success. This is most unfortunate for, from a practical standpoint, the several metabolic functions of the liver are of much more significance than is its excretory function. Fortunately for the individual with hepatic disease, however, the enormous functional reserve and remarkable regenerative capacity of that organ enable it adequately to maintain its important metabolic activities even in the presence of advanced anatomical changes, particularly if the disease process is chronic in nature. For these reasons attention has been directed particularly toward the diagnostic significance of the van den Bergh reaction, the degree of bilirubinemia and the ability of the liver to eliminate halogenated phenolphthaleins from the blood stream. Bromsulphalein has proved to be the most satisfactory of the latter substances and has been employed extensively in recent years.

The present report constitutes an analysis of the positive findings

obtained by one or more of these methods in 224 determinations made upon 188 patients.

Van den Bergh Reaction. On the basis of differences in color reaction observed when icteric sera are treated with Ehrlich's diazo reagent (diazobenzosulphochlorid), van den Bergh¹ postulated the existence of two types or forms of combination of bilirubin in the blood of jaundiced individuals; one form, present characteristically in obstructive jaundice, was believed to give the so-called immediate direct reaction, forming acetophenolazorubin promptly upon the direct addition of the diazo reagent; the other form responded only after the precipitation of the serum or plasma proteins by alcohol, this type of reaction being supposedly characteristic of hemolytic jaundice. This view was supported by McNee,² who utilized this hypothesis as the basis for his conception of the liver lobule as a functional unit in the metabolism of bilirubin whereby the mechanism of production of obstructive hepatic jaundice, nonobstructive hepatic jaundice and hemolytic jaundice could be conveniently explained.

Clinical trial, however, did not appear to justify the belief that various types of jaundice could be accurately differentiated by this method. Varying responses obtained at different times in the same individual have tended to discredit the differential diagnostic value of the van den Bergh reaction. At present many are of the opinion that the type of response is determined solely by the concentration of bilirubin if certain factors such as temperature and hydrogen-ion concentration are controlled. Snider and Reinhold³ found that as increasing amounts of bilirubin were added to serum the direct van den Bergh reaction changed from negative to delayed, then to biphasic and immediate and, conversely, that dilution of icteric serum with normal serum changed the reaction from immediate to delayed. They conclude that the type of direct van den Bergh reaction observed in serum depends upon the concentration of bilirubin and is independent of the underlying cause of the existing hyperbilirubinemia. The degree of bilirubinemia (icterus index) associated with each type of van den Bergh reaction observed in the present series of patients is shown in Table 1. The van den Bergh reaction was performed according to the method suggested by Lepehne⁴ and the icterus index by the method of Bernheim.⁵

Hyperbilirubinemia (icterus index above 6) was present in all but 1 case (I. I. 3.9), its absence in this instance, in spite of obvious hepatic disease (confirmed at autopsy), being presumably due to the existence of a profound secondary anemia. The icterus index range in each group was as follows: positive indirect (negative direct) reaction, 3.9 to 21.8; delayed direct reaction, 12 to 48.8; biphasic direct reaction, 10 to 99; immediate direct reaction, 13.2 to 173.

TABLE 1.—BILIRUBINEMIA IN VAN DEN BERGH REACTION GROUPS.

Icterus index.	Cases.	Direct van den Bergh.			
		Negative.	Delayed.	Biphasic.	Immediate.
3.9	1	1			
6.1-10	44	42	..	2	
10.1-20	103	47	35	20	1
20.1-30	21	1	5	12	3
30.1-40	13	..	3	8	2
40.1-50	7	..	1	6	
50.1-60	12	6	6
60.1-70	3	3	
70.1-80	8	3	5
80.1-90	3	2	1
90.1-100	1	1	
100.1-120	2	2
120.1-140	4	4
140.1-180	2	2
Total	224	91	44	63	26

It is evident that considerable overlapping occurs in the different reaction groups. Grouping the negative direct and delayed direct reactions together, since they possess the same clinical significance, all of the cases of hyperbilirubinemia presenting these reactions exhibited icterus index values ranging from 6.1 to 50 (100 per cent). Of the 63 sera giving the biphasic direct reaction 48 (76.1 per cent) fall within the same icterus index range (6.1 to 50). Of the 26 sera giving the immediate direct reaction, 6 (23 per cent) fall within this range. If care is exercised in the performance of the test and in timing the color reactions there is certainly a sufficiently marked difference, particularly between the negative or delayed reactions and the biphasic or immediate reactions, to preclude the probability, suggested by Snider and Reinhold,³ that this overlapping may be satisfactorily explained on the basis of experimental error. Variations in temperature and hydrogen-ion concentration, although of theoretical significance, are of little practical importance under standard laboratory conditions.

These observations suggest that factors other than the concentration of bilirubin in the serum are involved in the determination of the type of van den Bergh reaction produced. This belief is further supported by an analysis of varying reactions occurring at different times in the same individual (Table 2).

There can be no question but that the transition from the stage of the indirect (negative direct) reaction through the stages of delayed, biphasic and immediate direct reactions is usually associated with a distinct tendency toward an increase in the degree of bilirubinemia. However, exceptions to this general rule were noted in 5 of the 19 cases in this group. In cases J. H., A. C., M. S. and C. M., a biphasic reaction occurred at an icterus index level lower than that associated, at another time, with a delayed reaction.

In case K. R. an immediate direct reaction was obtained at a lower bilirubin concentration than was present with a biphasic reaction.

TABLE 2.—VARIATION IN VAN DEN BERGH REACTION IN SAME INDIVIDUAL AT DIFFERENT TIMES.

Case.	Condition.	Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
		I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
A. C.	Comm. duct	34	35	236	30	40				
	Stricture	30					
J. H.	Carcinoma	9.1	15	162	37	20	180	24	20	210	60	20	230
	pancreas												
K. G.	Comm. duct	13	..	154						
	Adhesions	12	10	...	24	8							
K. R.	Comm. duct	75	54.9	50	
	Stone	60	60				
J. C.	Comm. duct	7.6	0	14.8	40				
	Stone												
A. S.	Comm. duct	10.9	0	37					
	Stone	11.2											
C. P.	Pernicious	9.0	..	88	13.3	..	92						
	anemia												
R. G.	Icterus	48.8	..	104						
	Neonatorum	8.4	18								
					15								
M. S.	Myocardial	20	15	138	17					
	insufficiency	21.4					
W. W.	Myocardial	12	30	...	13.7	35			25				
	insufficiency												
S. G.	Cholecystitis	9.2	10	188	59	80	240
	acute												
C. D.	Cholecystitis	9.2	0	...	17.7	0	300						
H. H.	Cholecystitis	11.6	15	...	12	15							
J. K.	Cholecystitis	11.6	3	...	12.1	5	164						
A. D.	Cholecystitis	10	..	136	63	..	150	129	80	136
	Cholelithiasis	12	20	42	80				
		13	8	33	80				
		13	5	142	33	50	184			
S. S.	Cholelithiasis	13.6	35	60	100	144			
F. C.	Cholelithiasis	9.9	0	26	35	141			
C. M.	Cholelithiasis	24	...	227	16	35				
					33	25							

* Dye retention in percentage.

† Cholesterol in milligrams per 100 cc.

Such discrepancies, particularly in the delayed and biphasic reactions, cannot be disregarded when attempting to evaluate the significance of the van den Bergh reaction. Results of dilution experiments such as those reported by Snider and Reinhold³ permit but limited deductions, as the concentration of variable factors, other than bilirubin, which might influence the response was not controlled. Other things being equal, it is well established that the diazo reaction varies in a definite manner with alteration in the bilirubin content of the serum. Barron⁶ found that when sodium bilirubinate, in buffered alkaline solution and giving an immediate direct reaction, is added to normal serum in amounts up to 12 mg. per 100 cc. an indirect (negative direct) reaction is obtained; with increasing concentrations up to 16 mg. per cent, biphasic, and above 16 mg. per cent, immediate direct reactions are produced. Barron concluded, as have others, that immediate coupling of the smaller amounts of bilirubin with the diazonium salt is prevented by the

adsorption of the pigment by some constituent of the serum, probably serum globulin. It was also noted that the preliminary or simultaneous addition of certain surface active substances, which prevent this adsorption of bilirubin, results in the production of an immediate reaction even in the presence of small quantities of bilirubin. From a clinical standpoint the most important of these surface active substances are the bile acids and cholesterol. Qualitative variations in the van den Bergh reaction may therefore presumably be dependent upon variations in the concentration of these factors as well as in that of bilirubin.

TABLE 3.—DEGREE OF BILIRUBINEMIA, BROMSULPHALEIN RETENTION AND CHOLESTEREMIA IN CONDITIONS OTHER THAN GALL-BLADDER DISEASE.

Case.	Condition.	Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
		I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
J. F.	Catarrhal jaundice	13.2	90	194
J. W.	Portal cirrhosis	10	20	165	18.1	70	162			
R. C.	Portal cirrhosis	54	35	96			
L. S.	Arsenical hepatitis	102	90	110
J. V.	Arsenical hepatitis	60	90	
											56	75	
C. Z.	Acute yellow atrophy	129	100	84
R. S.	Acute hepatitis	75	80	182
M. M.	Acute hepatitis	10.1	0	...	25.9	80	176						
					17	25							
J. M.	Acute hepatitis	18.8	60	...	80	95	148
G. T.	Acute hepatitis	60	50	180			
S. L.	Acute hepatitis	43	40	142			
F. L.	Myocardial failure	15.5	5	...						
E. Y.	Myocardial failure	16	0	176						
W. W.	Myocardial failure	12	30	166	13.7	30	...	17	15	...			
M. S.	Myocardial failure	20	5	138						
A. S.	Myocardial failure	11.2	5	376	15	0	...	26	30	
W. M.	Myocardial failure	15.0	0	...			
J. G.	Myocardial failure	33	20	...			
H. L.	Banti's disease						
O. P.	Banti's disease	12.8	0	105						
J. C.	Banti's disease						
I. C.	Banti's disease	11.1	10						
S. T.	Pernicious anemia	16	0	100						
C. P.	Pernicious anemia	9	0	104	13.3	0	96						
A. P.	Pernicious anemia	14.1	0	...						
A. H.	Pernicious anemia	14.4	0	...						
J. H.	Hemolytic jaundice	12	0	110						
C. G.	Icterus neonatorum	12	0						
K. G.	Icterus neonatorum	8.4	0	...	18	0	...						
J. K.	Acute leukemia	13.8						

* Dye retention in percentage.

† Cholesterol in milligrams per 100 cc.

In this series there is no apparent correlation between the plasma cholesterol content and the type of van den Bergh reaction (Tables 2, 7 and 8). Examination of the data reported by Meyer⁷ in a study of liver function in diabetes mellitus likewise reveals no such correlation. Unfortunately, no satisfactory method is yet available

for the quantitative determination of bile acids in blood, so that the influence of that factor in clinical conditions cannot be accurately investigated. Analysis of the data presented in Table 2, however, appears to indicate that the state of hepatic function, as evidenced by the degree of retention of bromsulphalein, may play an important part in determining the type of reaction. It may be noted that in those instances in which a biphasic reaction was produced at a lower level of bilirubinemia than a delayed reaction the degree of bromsulphalein retention was invariably greater at the time the former response was obtained. Although the underlying cause of the change in reaction remains in doubt, these observations support the view originally held with regard to the clinical significance of the biphasic direct reaction as being indicative of hepatic functional impairment. In Table 3 are presented the findings in cases of hepatic cirrhosis, acute toxic necrosis of the liver, hepatitis, myocardial failure, pernicious anemia, Banti's disease and hemolytic icterus. It is of interest to note that in one patient with catarrhal jaundice an immediate direct reaction was obtained with an icterus index of 13.2.

TABLE 4.—CARCINOMA OF PANCREAS.

Case.	Direct van den Bergh.											
	Negative.			Delayed.			Biphasic.			Immediate.		
	I. I.	Dye.*	Chol.†	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
J. H.	9.1	15	162	37	20	180	24	20	210	60	20	230
A. C.	30	10	210	74	25	236
							30	15	214			
L. G.	66	40	234			
H. G.	84	30	192			
							99	30	202			
C. B.	76	30	
H. C.	108	60	348
H. D.	173	90	224
M. W.	85.7	35	246
										34.5	20	197
E. F.	30	30	184

* Dye retention in percentage.

† Cholesterol in milligrams per 100 cc.

The conclusion seems justifiable that repeated determinations of the van den Bergh reaction and the observation of its transition from one type to another in individuals with biliary tract disease are of considerable significance if interpreted in conjunction with estimations of the degree of bilirubinemia and bromsulphalein retention. As stated by Barron,⁶ although the diazo reaction behaves in severe nonobstructive jaundice just as in obstructive jaundice, it differs in that in the former case the transition from a negative or delayed direct reaction is relatively slow, occurring only

in consequence of hepatic polygonal cell destruction, whereas in the latter the change takes place rapidly, frequently within a few hours after complete obstruction has occurred. The qualitative phase of the van den Bergh reaction is deserving of more clinical study than has recently been devoted to it.

Bromsulphalein Retention. The bromsulphalein dosage employed was 2 mg. per Kg. of body weight, with which quantity no 30 minute retention has been observed in large numbers of control studies in individuals without biliary tract disease.

In many of the reported studies of the bromsulphalein test the statement is made that, except in portal cirrhosis, retention of the dye occurs only in the presence of hyperbilirubinemia, the degree of retention of dye and pigment being approximately parallel. This conclusion was reached by Piersol and Rothman⁸ and by Foley.⁹ The data presented by the latter, however, also indicate a disproportionately high degree of dye retention in patients with myocardial failure and passive congestion of the liver. The present series contains an unusually large number of cases in which the degree of bromsulphalein retention was out of all proportion to the bilirubin concentration of the blood serum. The majority of these findings were in patients with cholecystitis with and without cholelithiasis. The most striking examples of these observations are presented in Table 5. It may be noted that in 3 cases 100 per cent retention of the dye occurred in individuals with icterus index values of 8.3, 7.2 and 8.7, respectively (cases B. A., E. T. and W. V.). The presence of hepatic functional insufficiency in these 3 cases was further evidenced by the high concentration of urobilinogen in the urine (1 to 150, 1 to 100 and 1 to 200 respectively). Physical examination revealed no evidence of hepatic enlargement, the diagnosis being subsequently confirmed at operation. The question of bromsulphalein retention in gall-bladder disease will be considered below. It is obvious, however, from these data, that the bromsulphalein test may be of great practical value in determining the operative risk and the most suitable time for operative intervention in surgical disorders of the biliary tract associated with but mild hyperbilirubinemia. Cases such as those represented in Table 5 are unquestionably complicated by impairment of hepatic functional efficiency which, if unrecognized, may lead to serious postoperative consequences. Under such circumstances the glycogenic function of the liver is usually impaired, as indicated in a study of ether hyperglycemia reported by Gehret and the author,¹⁰ although the methods available clinically for the estimation of this important function usually fail to disclose evidence of serious disturbance (glucose, levulose and galactose tolerance tests).

In Table 6 are presented data which further illustrate the lack of correlation between icterus index values and the degree of bromsulphalein retention in certain cases. Repeated observations in the

same case may reveal independent variations in these two factors, indicating an apparent dissociation of two phases of a single function, excretion; *i. e.*, the ability of the liver to excrete bilirubin, a normal excretory product, may vary independently of its capacity for eliminating bromsulphalein, a foreign substance.

TABLE 5.—BROMSULPHALEIN RETENTION WITH LITTLE OR NO HYPERBILIRUBINEMIA.

Case.	Condition.	Direct v. d. B.	I. I.	Dye.*	Chol.†	Urobilinogen.
M. D.	Cholecystitis (stone)	Negative	9.8	35	146	1-60
A. D.	Cholecystitis (stone)	Negative	10.0	20	150	
M. R.	Cholecystitis (stone)	Negative	7.8	50	198	1-40
		Negative	6.2	20		
		Negative	8.1	20	347	
		Negative	7.4	20		
M. S.	Cholecystitis (stone)	Negative	8	20	...	1-30
B. A.	Cholecystitis (stone)	Negative	8.3	100	162	1-150
E. S.	Cholecystitis (stone)	Negative	8.4	10	165	
		Negative	8.6	10		
S. G.	Cholecystitis (acute)	Negative	9.2	10	188	
E. T.	Cholecystitis (chronic)	Negative	7.2	100	210	1-100
		Negative	7	5	...	1-40
W. V.	Cholecystitis (chronic)	Negative	8.7	100	226	1-200
N. H.	Cholecystitis (chronic)	Negative	7.4	10	156	1-350
J. M.	Cholecystitis (chronic)	Negative	6.7	30	...	1-80
V. R.	Cholecystitis (chronic)	Negative	9.6	10		
H. H.	Cholecystitis (chronic)	Negative	7	10	...	1-40
P. M.	Cholecystitis (chronic)	Negative	8.9	20	180	
		Negative	9.9	15	184	
A. D.	Cholecystitis (chronic)	Negative	8	10		
J. W.	Portal cirrhosis	Negative	10	10		
W. M.	Myocardial failure	Negative	9.2	10		
L. R.	Alcoholism	Negative	8	15		
M. G.	Duodenitis	Negative	8.8	20		
S. S.	Duodenitis	Negative	9.7	10	202	
G. J.	Adrenal neoplasm	Negative	3.9	10		

* Dye retention in percentage. † Cholesterol in milligrams per 100 cc.

TABLE 6.—INDEPENDENT VARIATION OF BROMSULPHALEIN RETENTION AND BILIRUBINEMIA.

Case.	Condition.	I. I.	Dye.*	I. I.	Dye.	I. I.	Dye.	I. I.	Dye.
A. D.	Cholecystitis (stone)	10	0	12	20	13	8	13	5
		42	80	33	80	33	50		
M. R.	Cholecystitis (stone)	7.8	50	6.2	20	8.1	20	7.4	20
E. T.	Cholecystitis (chronic)	7.2	100	7.0	5				
P. M.	Cholecystitis (chronic)	12	5	8.9	20	9.9	15		
H. V.	Arsenical hepatitis	102	90	60	90	56	75		

* Dye retention in percentage.

Cholecystitis and Cholelithiasis. In this series of 188 patients presenting either hyperbilirubinemia or bromsulphalein retention or both, there were 70 individuals with gall-bladder disease, 34 of

whom were suffering with chronic cholecystitis, 4 with acute cholecystitis and hepatitis, 26 with cholelithiasis and 6 with chronic cholecystitis complicated in 4 instances by chronic hepatitis, in 1 by obstructive biliary cirrhosis and in 1 by diabetes mellitus. In all cases the diagnosis was made by cholecystography supplemented, in most instances, by biliary drainage. In the majority of cases the diagnosis was subsequently established by operation. In the period of 32 months covered by these observations, similar studies, with negative results, were made upon 164 additional patients with

TABLE 7.—CHRONIC CHOLECYSTITIS.

Case.	Direct van den Bergh.*					
	Negative.			Delayed.		
	I. I.	Dye.†	Chol.	I. I.	Dye.	Chol.
C. C.	20	5	186			
M. D.	11.4	20	194			
E. D.	11.2	10				
E. F.	13.2	10	
J. H.	12	10	12	15	160
F. H.	12	0	
N. H.	7.4	10	156			
J. K.	11.6	3	12.1	5	164
A. R.	13.2	20	184			
E. S.	12	30				
E. B.	8.6	5				
E. T.	7.2	100	210			
	7.0	5				
W. V.	8.7	100	226			
H. L.	18	20	160
P. M.	12	5	180			
	8.9	20				
	9.9	15	184			
F. M.	9.1	5	126			
T. M.	9.4	5				
M. M.	12	0	176
W. P.	12.7	10	180			
H. P.	18.4	0	180
J. S.	12	5	190			
F. M.	9.6	5	160			
M. M.	9.4	5	140			
J. P.	12.4	0	190			
L. J.	12.3	10	154			
G. G.	14.8	20	162
F. C.	12.8	10	180			
D. D.	9.2	0	17.7	0	300
C. C.	8.1	5	190			
	10	15	184			
E. Z.	12	10	180			
G. K.	13.2	20	243
J. M.	6.7	30				
V. R.	9.6	10				
H. H.	7	10				

* There were no biphasic or immediate reactions in this group.

† Dye retention expressed in percentage.

gall-bladder disease. In our experience, therefore, approximately 30 per cent of all individuals with gall-bladder disease, whether or not associated with cholelithiasis, manifest either hyperbilirubinemia or bromsulphalein retention or, in most cases, both. The data pertinent to this group are tabulated in Tables 7, 8 and 9.

TABLE 8.—CHOLECYSTITIS AND CHOLELITHIASIS.

Case.	Direct van den Bergh.											
	Negative.			Delayed.			Biphasic.			Immediate.		
	I. I.	Dye.*	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
G. D.	50	20	210			
M. D.	9.8	35	146									
A. D.	10	20	136	63	80	150	129	80	136
	12	20	42	80				
	13	8	33	80				
	13	5	142	33	50	184			
A. F.	27.4	0							
C. G.	56.3	50	222			
R. K.	13.1	30	...	16	60	157			
L. K.	32	50	254			
M. R.	7.8	50	198									
	6.2	20										
	8.1	20	347									
	7.4	20										
M. R.	37	20	210			
D. S.	14	15	240			
M. S.	8	20	146									
S. S.	13.6	30	60	100	144			
A. W.	11.8	5	147									
B. A.	8.3	100	162									
M. C.	12	0	188						
F. C.	9.9	0	26	30	141			
M. D.	10.4	5	168									
E. S.	8.4	10	165									
	8.6	10										
C. M.	24	..	227	16	30				
				33	25							
J. P.	20	40	194						
A. R.	13.2	15	184									
R. W.	11.8	10	147									
M. Z.	7.8	5										
	11.2	35	205									
F. N.	37	15	245			
S. S.	8.7	5	186									
W. D.	40	30	226

* Dye retention expressed in percentage.

In the cases of chronic cholecystitis uncomplicated by cholelithiasis or clinically demonstrable hepatic disease the van den Bergh reaction was either indirect (negative direct) or delayed direct, the degree of bromsulphalein retention varying from 0 to 100 per cent. In the patients with acute cholecystitis and hepatitis,

cholelithiasis, or chronic cholecystitis associated with hepatitis or cirrhosis, reactions of all varieties were observed, varying in some instances in the same individual, as illustrated in Table 2.

TABLE 9.—CHOLECYSTITIS WITH COMPLICATION.

Case.	Complicating condition.	Direct van den Bergh.											
		Negative.			Delayed.			Biphasic.			Immediate.		
		I. I.	Dye.*	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.	I. I.	Dye.	Chol.
H. F.	Chronic hepatitis	13.2	25	104	12.5	30	200			
L. L.	Chronic hepatitis	20.	40	110			
M. C.	Acute hepatitis	46 8	90	94			
T. D.	Acute hepatitis	75	100				
M. D.	Acute hepatitis	18 8	40	...	132		
J. M.	Acute hepatitis				80	..	148
A. L.	Chronic hepatitis	10	5										
		10.4	..	192									
S. G.	Chronic hepatitis	9.2	10	188	59	80	240
C. O.	Diabetes	11.5	20	280									
N. M.	Cirrhosis	42	40	120	162	60	164
								56	..	77			

* Dye retention expressed in percentage.

Greene, Snell and Walters¹¹ noted that in experimentally produced obstructive jaundice, bromsulphalein retention roughly paralleled the degree of bilirubinemia. In the present series this relationship is maintained to a certain extent in clinical obstructive jaundice if such cases are compared with one another (Tables 4 and 8). It is apparent, however, that dye retention may occur in patients with chronic cholecystitis at much lower levels of bilirubinemia than in obstructive jaundice, particularly if due to carcinoma of the pancreas with relatively little hepatic functional disturbance. In individuals with cholelithiasis and common duct obstruction due to stone, superimposed upon the conditions which are common to all cases of obstructive jaundice are those associated with chronic cholecystitis, which may include hepatic functional insufficiency with consequent higher grades of bromsulphalein retention than may occur in pancreatic carcinoma with the same serum bilirubin content.

These findings in gall-bladder disease are not in accord with data reported by most investigators, which appear to indicate that bromsulphalein retention does not occur in cases of chronic cholecystitis without stone or clinically demonstrable hepatic disease. The statement is also frequently made that under such circumstances hyperbilirubinemia is not observed.

In our experience the chief practical significance of the van den Bergh reaction, the bromsulphalein test and the icterus index determination lies in the fact that abnormal findings may and do occur in a considerable proportion of patients with chronic cholecystitis, with or without cholelithiasis, without other clinical evidence of disturbed hepatic function. If the observations of Rosenthal and

White,¹² indicating that the degree of bromsulphalein retention is proportional to the amount of hepatic tissue removed from experimental animals, are applicable to clinical conditions, it would seem that in certain cases of gall-bladder disease with but slight impairment of the bilirubin excretory function, the greatly diminished capacity of the liver for eliminating bromsulphalein is comparable to that which would occur in organic disease involving practically all of the functioning hepatic tissue. The basis for the existing impairment of hepatic function in these individuals is difficult to determine. The disturbance must be widespread, involving a considerable portion of the liver, and nevertheless, must be readily amenable to correction, since essentially normal findings may be obtained within a relatively short space of time following the institution of proper therapeutic procedures. These criteria suggest that the hepatic disorder is largely "functional" in nature, secondary to organic disease of the gall bladder or bile ducts and associated, if with any, with but slight organic disease of the liver parenchyma. Failure to recognize the presence and significance of hepatic dysfunction in such cases is responsible for much of the postoperative morbidity and mortality of biliary tract surgery.

Summary and Conclusions. 1. Analysis of observations on the degree of bilirubinemia, bromsulphalein retention and the van den Bergh reaction in a group of 188 patients showing abnormal response to one or more of these studies appears to indicate that the type of diazo reaction is not determined solely by the serum bilirubin content.

2. The type of van den Bergh reaction appears to bear a more direct relation to the degree of bromsulphalein retention than to the degree of bilirubinemia except in cases of extra-hepatic obstructive jaundice.

3. There is no direct correlation between the type of van den Bergh reaction and the plasma cholesterol concentration.

4. Repeated determinations of the van den Bergh reaction and the observation of its transition from one type to another in individuals with biliary tract disease are of considerable significance, if interpreted in conjunction with the estimation of the degree of bilirubinemia and bromsulphalein retention.

5. Of 234 patients with cholecystitis with and without cholelithiasis, 70 presented either hyperbilirubinemia or bromsulphalein retention or both. Of these, 34 were cases of chronic cholecystitis, without cholelithiasis and with no other demonstrable evidence of hepatic disease.

6. In 3 cases of gall-bladder disease there was 100 per cent retention of bromsulphalein at the end of 30 minutes, associated with icterus index values of 8.3, 7.2 and 8.7. These findings suggest dissociation of these two phases of the excretory function of the liver.

7. This disturbance of hepatic function in patients with gall bladder disease appears to be largely "functional" in nature and associated with but slight demonstrable organic disease of the liver parenchyma.

8. More careful routine preoperative study of patients with surgical disorders of the biliary passages and proper preoperative treatment will perhaps greatly diminish the postoperative morbidity and mortality of biliary tract surgery.

BIBLIOGRAPHY.

1. van den Bergh, H.: *Der Gallenfarbstoff im Blute*, Leiden, 1918.
2. McNee, J. W.: Jaundice; a Review of Recent Work, *Quart. J. Med.*, 1922-1923, **16**, 390.
3. Snider, H. F., and Reinhold, J. G.: A New Interpretation of the van den Bergh Reaction, *Am. J. Med. Sci.*, 1930, **180**, 248.
4. Lepehne, G.: Zur Chromodiagnostik der Leber, *Berl. klin. Wehnschr.*, 1921, **58**, 1437.
5. Bernheim, A. R.: Icterus Index (A Quantitative Estimation of Bilirubinemia): Aid in Diagnosis and Prognosis, *J. Am. Med. Assn.*, 1924, **82**, 291.
6. Barron, E. S. G.: Bilirubinemia, *Medicine*, 1931, **10**, 77.
7. Meyer, E. L.: Function of the Liver in Diabetes Mellitus, *Arch. Int. Med.*, 1931, **47**, 182.
8. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, *J. Am. Med. Assn.*, 1928, **91**, 1768.
9. Foley, E. F.: The Clinical Value of Tests of Liver Function, *Arch. Int. Med.*, 1930, **45**, 302.
10. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia with Special Reference to Hepatic Disease, *J. Am. Med. Assn.*, 1931, **96**, 939.
11. Greene, C. H., Snell, A. M., and Walters, W.: Diseases of the Liver: Survey of Tests for Hepatic Function, *Arch. Int. Med.*, 1925, **36**, 248.
12. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test of Hepatic Function, *J. Am. Med. Assn.*, 1928, **84**, 1112.

CLINICAL REACTIONS TO VACCINES AS GUIDES IN TREATMENT.*

BY WILLIAM S. THOMAS, M.D.,

ASSOCIATE ATTENDING PHYSICIAN AND DIRECTOR OF ALLERGY CLINIC,
ST. LUKE'S HOSPITAL,

AND

M. D. TOUART, M.D.,

MEDICAL DIRECTOR, GRASSLANDS HOSPITAL AND CHIEF OF ARTHRITIC CLINIC,
FRENCH HOSPITAL, NEW YORK CITY.

(From the Departments of Immunology of St. Luke's Hospital and the French Hospital.)

A RECENT reporter¹ tells of four British pathologists of repute who recommended dosages of autogenous streptococcal vaccines in amounts so variable as are the figures 1 and 27,000. "After this,"

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he comments, "one cannot wonder that many scoff at vaccine treatment." Perhaps the poor repute in which vaccine therapy is held by so many clinicians may be due in part to the fact that its aid has been sought rather indiscriminately. Thus, in Murray's² opinion, not much importance should be placed upon the dissatisfaction with vaccines cited by Irons,³ because it is believed that at the time of his investigation vaccines were being indiscriminately employed, whereas today recourse to this form of therapy is being restricted more properly to suitable patients. Another reason may be that there has been in some cases a lack of thoroughness in observing the minutiae of the effects of vaccine injections as guides in treatment. Lieb⁴ thinks that most of the cases of failure of vaccine therapy are due to improper composition and preparation of the material used or to its faulty administration. He holds that results can be improved by better methods of selecting the bacteria and by better control of the dosage, and he insists that patients should be submitted to a rigid cross examination as to previous reactions before decision is made upon each treatment injection. Hicks⁵ recalls the fact that many users of vaccines in the past administered them by rule of thumb at stated intervals and hoped for the best. He is convinced that many of the failures of vaccine therapy are due to lack of appreciation of the extreme variability in the sensitiveness of an individual to his vaccine. Kolmer⁶ also upholds these principles and feels that such therapy is worthy of further use when conducted with due regard for important technical details of preparation and administration of vaccines.

It is the desire of the present writers, by describing a method of performing vaccine skin tests and of interpreting their reactions, to help improve the technique of vaccine therapy, especially in the case of patients sensitized to bacterial substances. The essential basis of the presentation is clinical experience; a discussion of theoretical questions is purposely reserved for a later communication.

It appears that vaccine skin tests, when properly conducted, may afford accurate information concerning the reactivity of a human being to bacteria, whether the testing material be made from organisms existing in his body or derived from other sources. In order to obtain and use such information to advantage it is necessary to know for what phenomena to look, to record those reactions that may occur and to apply the knowledge thus obtained to the subsequent conduct of the case. It has come to be thought that no observations made upon laboratory animals or upon test-tube reactions can tell so unerringly as can vaccine reactions, whether or not a particular strain of organism is harmful to a certain individual or whether it should be employed as a vaccine in treating the symptoms that may exist.

Inquiries among clinicians who employ vaccine therapy, however, have revealed the fact that but few of them make use of skin tests

as guides and that, among the few who do so, there exists a striking dissimilarity in the methods of observation and of evaluating the significance of the reactions obtained. The establishment of standards of procedure and of interpretation of vaccine reactions should place them upon a recognized basis similar to that occupied by other biologic tests which employ the human skin in place of the microscope or test-tube. The tuberculin test, the Schick and Dick tests have found their place in modern medicine and so, also, it is believed, should vaccine tests, and especially autogenous vaccine tests.

It is purposed, therefore, to describe some of the reactions which have been observed and to endeavor to evaluate their significance as guides in treatment, in the light of 12 years' work in this field. A little fewer than 900 patients who underwent vaccine skin tests received a total number of more than 13,000 vaccine injections. They were, for the most part, persons suffering with asthma, allergic coryza, allergic dermatoses and infectious arthritis. Out of this clinical material there have been collected the case histories of all the patients with asthma supposed to be bacterial in origin, who have been tested and treated with autogenous vaccines. These case histories, 328 in number, furnish the data upon which this presentation is based. Observations made upon the 888 vaccine-tested patients have also contributed their share to opinions held by the present writers, but all numerical statistics are based solely upon information derived from the records of the smaller group.

The 328 asthmatic subjects are of two classes: (1) Those who failed to react positively to full protein tests, and (2) those who, although shown to be sensitive to external allergenic agents, remained unrelieved of their asthma after avoidance of contact with all known offending allergens. The division of asthmatic patients into the two classes of so-called sensitive and nonsensitive cases has been made in order to separate those reacting positively to external proteins from those whose symptoms are due to infection or to unknown causes. This classification appears to be no longer justified in the light of the present-day recognition of bacterial allergy. The fact should be borne in mind that the manifestations of allergy may differ widely according to the species of animal affected and to the nature of the allergic agent.

Twenty-eight patients among this group of individuals reacted negatively to autogenous vaccine skin tests based upon a complete bacterial survey and therefore did not receive vaccine treatment. Two additional negative vaccine reactors did receive vaccine treatment for the purpose of study and their data are included in the series of 300 vaccine-treated asthmatic patients.

The method of vaccine testing which has been evolved consists of isolating in pure culture and preparing as vaccines^{7,21,24,27} all culturable organisms with the exception of spore bearers. The basic

requirement is a thorough bacteriologic examination of materials from all possible foci of infection. Attention is chiefly directed to a study of materials from the nares and accessory sinuses, nasopharynx and tonsils, sputum from the deeper air passages and, if necessary, of the feces. In each case the testing vaccine was a 1 per cent suspension of heat-killed bacterial substance⁸ in physiologic saline solution with an added phenol derivative as a preservative. The intradermal injection was made with a tuberculin syringe armed with a fine needle. The amount of suspension used for each test was regularly 0.01 cc. A control test with the diluent was always made. Rarely patients were encountered who reacted positively to the phenol derivative. The testing dose of the vaccine was the equivalent of 80 million bacteria of average streptococcus size. The reactions mentioned throughout this article are those such as may follow any vaccine injection, whether administered for testing or for treatment. All of the tests and, for the past 2 years, the majority of the treatment vaccines have been given by the intradermal route.^{6,9,10,11}

The use of the skin as a medium for tests with bacteria or their derivatives was inaugurated by von Pirquet in his experiments with tuberculin in 1907.¹² Gay and Force¹³ in 1913 made dermal tests with an extract of typhoid bacilli and found local late reactions in typhoid immunes. I. C. Walker, a pioneer worker in this field, made scratch tests upon asthmatic patients, using stock bacterial extracts in 1916.¹⁴ The early wheal reaction to bacterial proteins was the particular phenomenon to which he attributed significance at that time. In describing the late local reaction which has now come to occupy an important place, he wrote: "There is one other type of reaction which appears to be negative or only slight at the usual half-hour interval for reading the results, but the next day this cut appears not unlike a slight infection, the skin surrounding the cut is hot, very red and slightly elevated. Frequently the cut will contain pus which has always proved to be sterile. This type occurs only very occasionally and possibly it should not be called a positive reaction; a more accurate name for the present would seem to be a 'delayed reaction'."

Experiments with the bacterial scratch tests of Walker were made, but paucity of effects led to the adoption of the intradermal route. The results encouraged an active continuance of this research, which has been continued to the present time.

More recent writers have described reactions to bacteria and their derivatives, notably Price,¹⁵ Swift¹⁶ and his associates, Mackenzie and Hanger,¹⁷ Derick and Fulton¹⁸ and Coburn.¹⁹ They record both early and late skin reactions similar to those described herein.

At the outset of this work the interpretation of vaccine reactions^{20,21} was based upon an hypothesis to which experience has given sufficient support to warrant its acceptance, in part, at least.

This hypothesis assumes that those bacteria obtained by culture from a patient and which are the cause of his symptoms, especially if the latter are allergic in character will, when properly made into vaccines and injected into his skin, set up specific and significant reactions.²³ The presence of such reactions was and is taken to signify that the organism causing them should be used in treatment of the case provided that all other existing causes have been removed.

As the cases multiplied in number it became evident not only that vaccines cause skin reactions but that other clinical effects are encountered with more or less frequency. Some of these additional phenomena appear to corroborate the teachings of the skin reactions and may also serve as guides in the subsequent treatment. These other reactions will be described and the attempt will be made to appraise their significance. Certain of them appear to be specific and of useful significance when produced by autogenous vaccines. When heterogenous or stock vaccines are used in making skin tests, any reactions that may follow are considered to be equally specific in character and to show that the patient is sensitized to them. One exception to this statement may exist, perhaps, in the case of the so-called general toxic reaction, to be described below. It is not believed, however, that tests made with stock vaccines are of great diagnostic value under ordinary circumstances, because it is not shown that the organisms concerned are present in the patient's body. No more does a positive reaction to a ragweed pollen test made in December signify that an existing coryza is due to pollen.

Focal surgery, whether of the paranasal sinuses, tonsils or any other sites of infection, has received the first consideration in the treatment of all cases within the present category. The rhinologic or other surgeon has been depended upon to drain all infected foci if possible. *No delusion has been harbored to the effect that vaccine treatment can cure a focus of pus pent up in a bony cavity or elsewhere.* Indeed, when autogenous vaccines were administered to patients whose homologous foci of infection had not been eradicated or drained, there followed either symptomatic or focal reactions or both—the symptoms under treatment were aggravated. It has therefore become apparent that autogenous vaccine therapy is contraindicated in the face of a closed homologous and causative focus of infection. When it is possible for surgery to remove an infected focus which is the sole seat of the cause of symptoms, relief may be confidently expected to follow, at least for a time. The removal of foci, however, is looked upon as but the beginning and not the end of treatment.

After surgical relief of all infected foci has been accomplished, vaccine treatment appears to be at times the agent needed to supplement measures already taken and often completes or prolongs relief otherwise begun. In borderline cases, perhaps more frequently

encountered than any others, where there exist but slight or no apparent lesions of infection, but where there does exist (as for example, in so-called carriers) a sufficient quantity of allergenic bacterial substance within the patient's body to produce symptoms of sensitization—in the cases of this nature vaccine treatment has appeared to afford more or less permanent relief which would be otherwise unobtainable without continuous resort to palliative drugs.

If it now be assumed that properly conducted²¹ vaccine tests have been made upon a patient of the properly selected type, for what reactions shall one look—how shall these reactions be read and recorded and how shall vaccine treatment be guided by them? The subjoined descriptions of reactions and other answers to these questions are based upon data contained in the case histories of 300 asthmatic patients to whom allusion has been made earlier in this article. In observing skin reactions it seems that mere inspection of the site of the inoculation is not enough. Such reaction phenomena as local heat, itching, presence of a palpable though invisible nodule and tenderness are not recognizable by the eye alone, but they are of extremely frequent occurrence and are evidently indications that an important biologic process is taking place. Likewise enlarged, tender lymph nodes, malaise, fever, nausea, the onset or increase of allergic symptoms following and due to vaccine injections—all of these deserve to be recognized and appraised and their meaning applied to the planning of the subsequent treatment of any case in which they may occur.

Early Local (Wheal) Reaction. The early positive reaction at the site of injection of a vaccine is a wheal at least 0.5 cm. larger in diameter than any which may appear at the site of the control injection. It frequently has an irregular outline or even pseudopods and is often surrounded by a zone of erythema (areola). Itching may be present. The wheal reaction is at its height in from 10 to 30 minutes and fades soon thereafter. It was seen in two-thirds of the patients treated and occurred at one-third of all the injection sites in the present series of cases. It is encountered more frequently in asthmatic than in arthritic patients. It persistently occurs on retesting or reinjecting for treatment in spite of prolonged vaccine therapy and even after the symptoms under treatment have been relieved.

Significance of the Early Local (Wheal) Reaction. Occurrence of the early wheal reaction is taken to indicate that the vaccine causing it should be used in the treatment of the case. This reaction is of aid in determining subsequent dosage of the vaccine. Should the reaction be very marked, the treatment dose next following is not increased, other things being equal.

In order to record the wheal reaction the circumference of the wheal and of the areola are outlined upon the skin with pen and ink and numbered. When dry, the picture is transferred by contact





to a sheet of damp white blotting paper and this, when dry, is filed for record. The outline, drawn to a scale, of wheal and areola may be copied upon a graph (Fig. 1).

Name, J. D.

Date, March, 9, 1932.

Diagnosis, Asthma.

Intradermal Autogenous Vaccine Tests. By J. N.

No.	Organism and source.	One-half hour.	Skin reactions. Day.				Other reactions.
			2	3	4		
1	Control		R N	N	N		Asthma was worse during the first two days after the tests were made. (A symptomatic reaction.)
2	Staph. aureus Sputum		A T R N N	A T R N	T R N		
3	Strep. viridans Nares		A A T R N	A A T T R N	A A T R N N		
4	Bac. alkali- ligenes Stool		A R N	R	R		

N = Nodule 0.5 cm. in diameter; NN = nodule twice as large.

R = Redness. T = Tenderness.

A = Areola; AA = areola 2 cm. in diameter.

FIG. 1.—A Sample Record of a Vaccine Reaction.

Late Local Skin Reaction. The late positive reaction at the site of inoculation is not unlike the Schick reaction in appearance, but in order to observe it properly its component features are noted by touch as well as by sight and with the assistance of the patient's sensations as described in response to questioning. The sum total of the symptoms are recorded graphically as they appear, change and disappear during the days following the test. Any or all of the following symptoms have been observed at the testing site:

(1) An indurated nodule, slightly or not at all elevated above the surrounding surface of the skin and about 0.5 cm. in diameter or larger, sometimes lasting for several or even for many days. Long endurance of it has come to be looked upon as a favorable prognostic

sign if the vaccine treatment can be thoroughly carried out. (2) Redness of the skin over the nodule. (3) A surrounding zone of erythem (areola) from 1 to 10 or more centimeters in average diameter. (4) Tenderness on pressure, usually at the nodule only, but sometimes extending over the whole of an existing areola. (5) Heat at the injection site or over the whole of the areola, usually beginning in from 6 to 12 hours and lasting for 1 or 2 days. (6) Swelling of the whole areola. (7) Lymphangitis, beginning in from 8 to 12 hours and lasting for a day or two, has been observed in about 2 per cent of the patients who showed late local reactions. (8) Pustule or vesicle in the nodule. This is not due to infection, as repeated culturings have always proved sterile. (9) Pigmentation of the surface of the nodule occurs late and is not often seen. (10) Desquamation of the skin over the site of the disappeared nodule is not common but occurs so late that it has doubtless been overlooked at times. Very rarely a slough has occurred at the site of the inoculation.

The features of the late local reaction may be recorded upon a graph (Fig. 1), in which N denotes a nodule 0.5 cm. in diameter; NN or N2, a nodule twice as large. Redness of the nodule is denoted by the letter R; T indicates tenderness on pressure. The findings of the late local reaction are read and recorded upon at least 2 successive days following the test. A late reaction is considered to be positive when, in addition to any features occurring at the control site, there are present during 2 or 3 days, three or more of the component features named above. Such reactions as vesicles and ecchymoses are considered to be positive even though occurring alone, and to indicate that the organisms causing them should be used in vaccine treatment of the case. In general, a late positive reaction is not what is visible at any one time, but rather, the aggregate of symptoms due to the vaccine injection and observed by the operator and the patient during at least 2 days following the tests.

The late local reaction usually grows less or disappears on retesting during a course of vaccine injections. Its waning after repeated injections is taken to be a signal calling for a corresponding increase in the dosage.

Of the asthmatic patients, 272 gave late local reactions to one or more of the autogenous strains with which they were tested.

Significance of the Late Local (Skin) Reaction. A positive late local reaction is taken to indicate that the autogenous vaccine causing it should be used in the treatment of the case. A very marked late local reaction calls for a smaller amount of vaccine to be given in the next following therapeutic dose than does a slight reaction. During the course of a series of treatment injections each late skin reaction helps the operator to determine the amount and the time of the next vaccine dose.

General Toxic Reaction. This term has been selected to express the rather frequently seen symptom-complex following vaccine injections and characterized by malaise, nausea, drowsiness, feverishness and occasionally swollen and tender lymph nodes. Any or all of these symptoms may occur within from 4 to 12 hours after the administration of the vaccine. This reaction occurs only in conjunction with a positive late local reaction.

Significance of the General Toxic Reaction. It signifies that an overdose of vaccine has been administered. It does not appear to furnish evidence for or against a specific action of the vaccine causing it, but it is of aid in determining subsequent vaccine dosage.

Symptomatic Reaction. This name is applied to the onset or increase of allergic symptoms such as bronchospasm, urticaria, joint pains, etc., following within 48 hours after the administration of vaccine. This reaction occurs only in conjunction with a positive local reaction.

Significance of the Symptomatic Reaction. When symptoms under treatment are made worse by a vaccine injection it is obvious that an overdose has been given, and perhaps that an undrained focus of infection exists. The effect of the vaccine in such a case is clearly specific and experience has proved that if proper treatment can be carried out, benefit may be expected to follow. The symptomatic reaction is of aid in fixing upon subsequent vaccine dosage.

Symptomatic reactions were recorded in 37 of the cases treated. Once elicited, this reaction can be expected to occur again if the dose be large enough. It has been endeavored in such cases to keep the dosage below the amount that will cause a repetition of the symptomatic reaction. The ultimate result of vaccine therapy in the patients in whom this reaction was observed was almost uniformly favorable. The 4 patients who showed symptomatic reactions and yet were not relieved after vaccine treatment were 3 in whom there existed inoperable foci of infection, and 1 who was unwilling to continue with the treatment.

Relief Reaction (Temporary). In 45 of the patients quick relief followed the testing or other injection of vaccines. The relief obtained was either partial or complete and occurred within a few minutes or hours after the vaccine injection and lasted for hours or days or even longer. That this relief reaction was not a mere coincidence was shown by the fact that in several of the patients it was elicited on several occasions. In some of the patients this reaction was seen where a larger dose of the respective vaccine would be regularly followed by a symptomatic reaction (asthmatic attack).

Significance of the (Temporary) Relief Reaction. This reaction appears to indicate that a favorable dose of a specific desensitizing substance has been administered. It is therefore an aid in fixing upon subsequent dosage. This temporary relief reaction should

not be confused with the more gradually developing and usually more permanent good results following a successful course of vaccine treatment. Of the patients who exhibited this reaction all but 4 obtained good results from their vaccine treatment.

Focal Reaction. By this term it is intended to signify a lighting-up of symptoms of infection at the site from which the vaccine organisms were obtained. It appears, if at all, within from 4 to 12 hours after administration of the vaccine. It has been observed in but few—perhaps 6—of the patients, but the records are incomplete with regard to the incidence of this reaction.

Significance of the Focal Reaction. A focal reaction is thought to indicate that the vaccine causing it is specifically related to a focus of infection but is not necessarily connected with the allergic or other symptoms that are under treatment. It may indicate the need for focal surgery at a site hitherto unsuspected.

Symptomatic reactions, relief reactions and focal reactions are welcomed by the physician because they indicate that a specifically active vaccine has been found. Their absence, however, is no indication that favorable results of vaccine treatment will fail to occur. In the series of cases here presented, good results were obtained in 132 patients who showed neither the relief nor the symptomatic reaction.

Recurrent Local Reaction. This phenomenon consists of the reappearance of a faded late skin reaction, days or weeks after its disappearance. It follows in from 6 to 24 hours after the reinjection of a vaccine elsewhere on the patient's body. Its incidence has not been completely recorded as it has not been noted many times. It is probable that more careful observation would have disclosed its presence oftener than was the case.

Significance of the Local Recurrent Reaction. At present this reaction does not appear to afford information that may aid in planning subsequent vaccine treatment.

Negative Reaction. This term means, of course, the absence of local and constitutional effects from the injection of a vaccine. In 30 of the patients selected for vaccine testing no reaction followed autogenous vaccine skin tests and consequently vaccine treatment was withheld except that for the purpose of study vaccine therapy was carried out in 2 patients who showed only negative vaccine reactions. They apparently derived no benefit from their courses of inoculations.

Significance of the Negative Reaction. The absence of all reactions appears to indicate that the organisms used are harmless to their host and that they will be of no benefit in treatment and should not be so used. While the negative reaction to testing vaccine injections is taken to be a contraindication for the use of the respective vaccines in treatment, it is, of course, quite different in the case of negative reactions following treatment injections. Here the organisms used

are those that have previously produced positive reactions. Negative reactions to therapeutic injections of vaccines during the course of properly conducted vaccine treatment are the signal for an increase in the dosage.

In recapitulating the indications applicable to the details of vaccine dosage it may be said that an increase in the amount is called for by a very slight or absent local reaction. A repetition of the last preceding dose is indicated in the cases of: (1) Moderate local late reaction; (2) relief reaction. A decrease in vaccine dosage would follow: (1) A very marked late local reaction; (2) a general toxic reaction; (3) a symptomatic reaction; (4) a focal reaction.

Recording Methods. A graph is presented (Fig. 1) showing a plan for recording vaccine tests and their local results. In the specimen case there recorded an early local (wheal) reaction is seen to have occurred in the case of the test made with *Staphylococcus aureus* recovered from the patient's sputum. The degree of the early reaction here is shown as an indication that the organism causing it should be prepared as a treatment vaccine and be used in treating this patient. Corroborative reason for so doing is found in the record of the late local reaction where, on the second day there was a large red nodule with tenderness and an areola. These symptoms persisted as late as the fourth day.

The late local reaction to the test with *Streptococcus viridans* from the patient's nares was also positive, as is shown in the columns for the second, third and fourth days. Here the reaction was actually greater on the fourth day than on the third. Such a late increment, when observed, has usually been a reaction to strains of streptococci.²⁵ As a rule, however, the positive late local reaction is at its height on the second day following the test.

In accordance with the findings recorded in this graph a treatment vaccine would be ordered to be composed of *Staphylococcus aureus* and of *Streptococcus viridans*, each in a concentration of five units (an arbitrary standardization, explained elsewhere^{7,21,24,27}) to the cubic centimeter of diluent; that is to say, the equivalent of 400 million organisms of average streptococcus size. The initial dose of this vaccine would be 0.5 cc., given intradermally after the acute symptoms due to the testing injections had disappeared. This decrease in dosage from the amount of material employed in the tests is based upon the fact, noted in the graph (Fig. 1), that there was an increase of asthmatic symptoms (symptomatic reaction) following the tests. The amount of treatment vaccine prescribed for the first dose would be one-fourth of that contained in the testing dose. As was already stated, the dose ordinarily administered as a test amounts to 80 million bacteria of average streptococcus size, so that the first treatment dose here mentioned would contain 20 million bacteria of each of the strains contained in the vaccine and suspended in 0.05 cc. of the diluent. There appears

to be no way in which to determine the amount of vaccine most suitable for administration to any patient except by testing him with it. The greatest variability in the degree of reaction is seen in different patients. Some of them require relatively large doses while others are so extremely sensitive to their autogenous vaccines that minute doses produce violent effects upon them.

The interval between doses of vaccine¹³ is regulated in each case by the time of disappearance of the more acute symptoms of reaction due to the preceding injection. It is usually from 4 days to 1 week. The presence of a persistent nodule, if it be no longer tender, even though red, need not cause postponement of the succeeding vaccine dose. The same may be said of desquamation over the site of a former nodule and of a lingering icteric hue about it.

The vaccine unit suspension system of Famulener^{24,27} has been found to be a material improvement upon the more complicated and less exact manner of reckoning vaccine dosage by the bacterial count. The bacterial counts given herein are for the convenience of readers who are accustomed to estimate dosage in that way.

The degree of concentration of bacterial vaccines has been observed to affect their potency. A given amount of bacterial substance may produce more pronounced reactions when suspended in a large amount of liquid than if administered to a patient in highly concentrated form. This fact has also been observed by Small.²⁶ It should be borne in mind when ordering or administering vaccines.

The advantage of using a regular form of chart for recording the results of vaccine testing and treatment cannot be overestimated. Blank forms as used by the writers are shown in Figs. 1 and 2.

Date
Name
Diagnosis
Composition and source of vaccines used
Other Treatment and Notes

Day.	Dosage.	Local early reaction.	Local late reaction, N. R. T. A., etc.	General toxic reaction.	Symptomatic reaction.	Relief reaction.	Focal reaction.	Return reaction to	Negative reaction.	Remarks, clinical history, results, etc.

FIG. 2.—Form Used to Record Vaccine Treatment and Effects.

Tables 1 and 2 present in statistical form the results which followed treatment based upon and controlled by vaccine skin and other reactions in 300 patients with bacterial asthma. These results are presented in order to illustrate the advantage of using these reactions as guides in treatment.

TABLE 1.—RESULTS OF TREATMENT OF BACTERIAL ASTHMA IN 300 PATIENTS.

	Patients.	Percentage.
Completely relieved	121	40
Materially but not completely relieved	95	31
Unrelieved or but slightly relieved	84	29
Total	300	100

TABLE 2.—DURATION OF RELIEF IN THE 216 PATIENTS IN WHOM FAVORABLE RESULTS WERE SEEN.*

Time.	Patients.	Percentage.
1 to 3 months	20	9.2
4 to 6 months	54	35.0
7 to 11 months	22	10.1
1 to 3 years	96	44.4
More than 3 years	18	8.3
Unrecorded duration	6	3.0
Total number of patients completely or materially relieved	216	

* The known duration of relief is that reported by patients at their last visit or in response to follow-up letters.

TABLE 3.—VACCINE INJECTIONS.

Vaccine skin tests made*	2286
Treatment vaccine injections	6026
Total vaccine injections	8302

* Including cases in which more than one set of vaccine tests were made.

TABLE 4.—INCIDENCE OF VARIOUS TYPES OF VACCINE REACTIONS (328 ASTHMATICS, SUPPOSEDLY BACTERIAL IN NATURE).

	Patients.
Early local reactors	200
Late local reactors	272
Symptomatic reactors	37
(Temporary) relief reactors	48
Negative reactors	30

Incompletely Recorded.

Focal reactors
Recurrent local reactors
General toxic reactors

Summary. The present attitude of physicians toward vaccine therapy is presented, and attention is directed to the need of a guide in the selection of vaccines for therapeutic use and in the conduct of vaccine therapy.

The clinical reactions observed in 328 asthmatic patients, tested and treated with autogenous vaccines, were found to be useful as guides in therapy. These reactions, as observed, are described in

detail and are offered as criteria in the selection of proper vaccines for treatment and in determining dosage and the intervals between doses.

Great variability in the degree of reaction to vaccines is seen in different persons. Some of them require relatively large doses, while others are so sensitive to their autogenous vaccines that comparatively minute doses produce violent effects. Properly conducted skin testing offers the best means by which to ascertain suitable vaccine dosage.

Conclusions. The plea is made for the adoption of certain standard procedures in all cases in which the employment of vaccine therapy is contemplated, namely:

1. Careful selection of patients, so as to avoid attempting vaccine therapy in persons unfitted for the method.
2. A complete bacteriologic survey of the patients and the preparation of standardized vaccines from all the organisms recovered, except those that are spore bearers.
3. The performance of skin testing with all vaccines so obtained.
4. Careful observation, recording and interpretation of the reactions that follow such tests.
5. Application of the data thus obtained to the subsequent management of the cases.

BIBLIOGRAPHY.

1. London letter, *J. Am. Med. Assn.*, 1931, **96**, 1808.
2. Murray, E. G. D.: Some Difficulties in Immunization with Vaccines, *Canadian Med. Assn. J.*, 1931, **25**, 135.
3. Irons, E. E.: Facts and Fallacies Concerning Foreign and Vaccine Therapy, *J. Am. Med. Assn.*, 1931, **96**, 1289.
4. Lieb, C. W.: Studies in Intestinal Intoxication, *New York State Med. J.*, 1929, **29**, 1389.
5. Hicks, J. A. B.: Uses and Misuses of Vaccines, *British Med. J.*, 1931, **2**, 650.
6. Kolmer, J. A.: Principles of Vaccine Therapy, *Am. J. Clin. Path.*, 1931, **1**, 355.
7. Famulener, L. W.: The Preparation of Autogenous Vaccines, *J. Allergy*, 1929, **1**, 84.
8. Hopkins, J. G.: A Method for Standardizing Bacterial Vaccine, *J. Am. Med. Assn.*, 1913, **60**, 1615.
9. Besredka, A.: Rôle of the Skin in Infection and Immunity. *Immunity in Infectious Diseases*, Baltimore, Williams & Wilkins, 1930.
10. Editorial: Cutaneous Bacteriolysins, *J. Am. Med. Assn.*, 1930, **94**, 1139.
11. Tuft, L.: The Skin as an Immunizing Organ, *J. Immunol.*, 1931, **21**, 85.
12. Von Pirquet, C.: Diagnosis of Tuberculosis by Cutaneous Inoculation, *Berl. klin. Wchnschr.*, 1907, **44**, 644.
13. Gay, F. P., and Force, J. F.: Skin Reactions in Typhoid Immunes, *Univ. of California Pubs. in Path.*, 1913, **2**, 127.
14. Walker, I. C.: Studies on Sensitization of Patients with Asthma to Bacterial Proteins as Demonstrated by the Skin Reaction, etc., *J. Med. Res.*, 1917, **35**, 487.
15. Price, W. A.: Dental Infection, Cleveland, Clinton Publishing Company, 1923.
16. Swift, H., Derick, C. L., and Hitchcock, C. H.: Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, *Trans. Assn. Am. Phys.*, 1928, **43**, 193.
17. Mackenzie, G. M., and Hanger, F. M., Jr.: Allergic Reactions to Streptococcus Antigens, *J. Immunol.*, 1927, **13**, 41.
18. Derick, C. L., and Fulton, M. N.: Skin Reactions of Patients and Normal Individuals to Protein Extracts of Streptococci, *J. Clin. Invest.*, 1931, **10**, 121.

19. Coburn, A. E.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.
20. Thomas, W. S., and Touart, M. D.: Treatment of Asthma with Autogenous Vaccines, Arch. Int. Med., 1924, 34, 79.
21. Thomas, W. S., Famulener, L. W., and Touart, M. D.: Autogenous Vaccines in Diagnosis, with Especial Reference to Asthma, Arch. Int. Med., 1924, 34, 85.
22. Touart, M. D.: Autogenous Vaccine Skin Tests, J. Allergy, 1929, 1, 85.
23. Thomas, W. S.: Autogenous Vaccine Treatment of Asthma, Ibid., p. 86.
24. Famulener, L. W.: A Method for the Standardization of Autogenous Vaccines, Acta Pathologica et Microbiologica, 1930, 7 (suppl.), 3.
25. Andrews, C. H., Derick, C. L., and Swift, H.: Skin Response of Rabbits to Nonhemolytic Streptococci; Description of Secondary Reaction Occurring Locally After Intradermal Inoculation, J. Exp. Med., 1926, 44, 35.
26. Small, J. S.: Rheumatic Fever, II, Am. J. Med. Sci., 1928, 175, 655.
27. Famulener, L. W.: Preparation of Vaccines, J. Lab. and Clin. Med., 1932, 17, 538.

THE MEDICAL IMPORTANCE OF FOCAL INFECTIVE PROSTATITIS.

BY P. S. PELOUZE, M.D.,

ASSISTANT PROFESSOR OF UROLOGY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA.

It is rapidly becoming realized that arthritis of one form or another is the cause of more human morbidity than almost any other disease entity. If to this are added the many other bodily ills that often are due to those same causes that account for most cases of arthritis, one amasses a group of patients of staggering medical importance and touches what is unquestionably mankind's greatest single economic health burden. The truth of these statements is beyond serious questioning, and, yet, the general medical understanding of the subject leaves much to be desired. And because of this much needless suffering is allowed to take place, suffering that could rather simply be prevented.

Few etiologic concepts stand upon a firmer foundation than does the fact that most of these systemic manifestations are the direct result of the absorption of toxic materials from some focus of infection. The recognition of this and the human benefits accruing therefrom mark one of the most striking and brilliant forward steps in the modern medicine. And, though the advance has been great, there has been a definite lagging in certain directions. Certain focal infective areas have been thrown so much into the spotlight of medical attention that they have tended to obscure other foci that, though commonly secondary to them, have at times a place of equal importance. Particularly is this true in regard to infections of the prostate gland.

It can be said without fear of successful contradiction that in the male the outstanding focal infective triad is *teeth*, *tonsils* and *prostate gland*. The importance of the first and the second is in the mind

of almost every physician, but often the third is only dimly sensed, more often it is not even thought of or known. So true is this latter statement that in 100 unselected patients presenting all sorts of focal infective manifestations in which this infection was a causal factor the average duration of treatment before any prostatic studies whatever were thought of was astonishingly long (4.5 years). The shortest period of treatment before prostatic study was 1 month and the longest 22 years.

The importance of the search for prostatic infection in such cases is well shown by the fact that at least 72 per cent of all males presenting such symptoms have a definite infection in this gland, and most of them cannot be made permanently symptom-free so long as it persists. It is an easily proved fact that at least 35 per cent of all men beyond the age of 35 years carry such a focus of infection, and the observation that this percentage more than doubles in those with focal infective symptoms would suggest that much could be done in the way of the prevention of these disabling conditions if prostatic studies were made a routine in our health examinations of all adult males.

Much of the general neglect of prostatic studies is to be attributed to two things, *viz.*: (1) A rather widespread lack of knowledge regarding the etiology of such infections; (2) the fact that very little attention has been given to the subject from a focal infective standpoint by urologists themselves.

The outstanding misconception regarding the etiology of prostatic infections is the old and grossly erroneous belief that all such infections are of gonococcal origin. The extent to which this thought has become fixed in the medical mind is amply shown by the frequency with which the internist and general practitioner totally, and without study, rule out such infection merely on the patient's statement that he has never had gonorrhea. Nothing could stand upon a less scientific basis and the falsity of few beliefs is more easily shown. In the herein reported 100 focal infective patients in whom the writer demonstrated definite infection in the prostate gland only 2 had had an attack of gonorrhea within 20 years. Only 7 gave a history of ever having had gonorrhea. It thus can be seen upon what a slender thread the belief has hung.

A close study of the etiologic factors underlying such prostatic infections immediately throws it into the foreground that they rarely are primary infections. Their association with dental and tonsillar infections is outstanding. In this series of cases dental infections showed an incidence of 61 per cent and tonsillar 69 per cent. Not only were these foci present but it is everywhere in evidence that they were in by far the vast majority of cases the primary foci from which the prostate obtained its infection. That this is true is shown by the absence of gonorrhea in their histories and by the repeated observation that the prostatic infection almost never can be permanently cured so long as these other foci persist.

TABULATION OF 100 UNSELECTED CASES OF FOCAL INFECTIVE PROSTATITIS.

Initials.	Age.	Duration of symptom.s.		Arthritis.	Ocular lesions.*	Other systemic lesions.†	Infected tonsils.	Infected teeth.	Later tooth infections.	Reactions following marriage.
		Yrs.	Mos.							
S. E.	66	2	..	x	—	—	—	—	—	x
F. L. J.	47	15	..	x	—	—	x	—	—	—
R. B. T.	40	8	..	x	—	x	x	x	x	x
S. F.	40	2	..	x	—	—	x	x	x	x
F. W. B.	30	..	6	x	—	—	—	—	—	—
J. S. K.	52	3	..	—	x	x	x	x	—	x
W. T.	42	12	..	—	—	x	x	x	x	x
H. F.	30	10	..	—	—	x	x	—	—	—
P. M.	74	..	6	—	—	x	—	—	—	—
J. C. L.	36	3	..	—	—	x	x	—	—	x
C. K.	57	..	5	—	—	x	—	—	—	—
E. M. J.	49	6	..	—	—	x	x	x	x	—
A. R.	58	7	..	—	—	x	x	—	—	—
A. C.	55	..	1	—	x	—	x	—	—	x
C. D.	49	..	2	—	x	—	—	x	—	x
H. B. C.	45	3	..	—	x	—	x	x	x	x
J. G. C.	39	2	..	—	x	—	x	x	x	x
E. P. R.	53	..	3	—	—	—	x	x	x	x
A. D. Y.	62	..	6	x	—	x	x	x	x	x
R. D.	47	5	..	—	—	x	—	x	—	x
P. J.	68	3	..	x	—	—	x	x	x	x
T. D. W.	46	1	..	x	—	—	—	x	x	x
W. H. L.	73	1	..	—	—	x	—	—	x	—
M. C. L.	50	1	..	x	—	—	—	x	—	x
C. Y. L.	54	3	..	x	—	—	x	x	—	x
F. H.	58	1	..	x	—	—	x	x	x	x
G. B. C.	49	..	4	x	—	—	x	x	x	—
E. D. H.	38	15	..	x	—	—	x	—	—	x
P. S. G.	24	1	..	x	—	—	x	x	x	x
H. R. W.	61	3	..	x	—	—	x	x	x	x
S. W. S.	39	..	2	—	—	x	x	—	—	—
L. G.	25	1	..	—	—	x	—	—	—	—
T. H. C.	58	7	..	x	—	—	—	x	x	—
G. C.	25	4	..	x	x	—	—	—	—	x
G. H. B.	58	2	..	x	—	—	—	—	—	—
C. B.	47	3	..	x	—	—	—	x	—	—
J. H. H.	47	9	..	x	—	—	x	—	—	—
W. E. C.	48	..	9	x	—	—	x	x	x	x
F. J. L.	33	6	..	x	—	—	x	x	x	x
W. W. B.	36	8	..	x	—	—	x	x	x	x
L. M. U.	50	2	..	—	—	x	—	—	—	—
A. Z.	29	5	..	—	—	x	x	—	—	—
C. H. M.	61	2	..	—	—	x	x	—	—	—
W. C. S.	50	3	..	—	—	x	x	—	—	—
H. M. C.	62	15	..	x	—	—	—	x	x	x
O. J. S.	48	1	..	x	—	—	x	x	—	—
W. W.	49	20	..	x	—	—	—	—	—	—
E. L. B.	55	12	..	x	—	—	x	—	—	x
M. C. D.	55	3	..	—	—	x	x	x	—	—
C. E. W.	68	20	..	x	—	—	—	—	—	x
W. H. B.	57	12	..	x	—	—	—	—	—	x
G. B.	58	5	..	x	—	—	x	x	—	x
A. B.	28	1	..	x	—	x	x	—	—	—
E. C. D.	39	10	..	x	—	x	x	—	—	—
L. W.	39	..	9	x	—	—	x	x	x	x
R. P. B.	60	2	..	x	—	—	x	x	x	x
W. A. A.	31	4	..	x	—	—	x	x	—	—
F. C.	51	..	1	x	—	—	x	x	—	x
W. F. B.	54	1	..	x	—	x	x	x	x	x
M. G.	61	6	..	x	—	x	—	—	—	—
A. G.	55	20	..	—	—	—	—	—	—	x
J. H.	42	..	2	x	—	—	x	—	—	—
B. G. H.	64	..	4	x	—	—	—	—	—	—
W. B. W.	52	..	1	—	—	x	x	—	—	x

TABULATION OF 100 UNSELECTED CASES OF FOCAL INFECTIVE PROSTATITIS.
(Continued.)

Initials.	Age.	Duration of symptoms.		Arthritis.	Ocular lesions.*	Other systemic lesions.†	Infected tonsils.	Infected teeth.	Later tooth infections.	Reactions following massage.
		Yrs.	Mos.							
W. W. R.	51	1	1	x	—	—	x	x	x	x
R. S.	48	1	..	—	—	x	x	—	—	—
S. T.	62	15	..	x	—	—	x	x	—	x
T. M. T.	56	4	..	x	—	—	x	x	—	x
D. F. V.	70	1	..	—	—	x	—	x	x	x
J. O.	26	..	4	x	—	—	—	x	x	x
J. L. P.	65	5	..	x	—	—	x	x	x	—
J. F. B.	27	11	..	x	—	—	x	—	—	—
R. M. C.	39	10	..	x	—	—	x	—	—	—
W. B. B.	50	..	3	x	—	—	x	—	x	x
E. F. J.	41	4	..	x	—	—	x	x	—	—
H. M. W.	53	2	..	x	—	—	x	—	—	—
W. M. M.	23	4	..	x	—	—	x	—	—	—
C. D.	49	2	..	—	x	—	x	x	x	x
J. G.	39	9	..	—	x	—	x	x	x	x
F. A. C.	53	..	1	—	x	—	x	x	x	x
R. J. B.	37	22	..	x	—	x	x	x	x	—
S. R. B.	46	..	2	—	x	—	x	x	—	—
A. A.	38	1	..	x	—	x	—	—	—	—
W. T. B.	54	1	..	x	—	—	x	—	—	—
G. F. D.	52	3	..	x	—	—	x	x	x	—
G. H. P.	62	..	3	x	—	—	—	x	x	—
R. Y. S.	48	..	8	—	—	x	—	x	—	—
W. C. S.	65	2	..	—	—	x	—	x	—	—
L. N.	48	..	4	x	—	—	x	—	—	—
G. M.	65	1	..	x	—	x	—	x	x	x
J. F.	43	5	..	x	x	—	x	—	—	x
F. S.	45	..	7	x	—	—	x	x	x	x
E. R. K.	41	15	..	x	x	—	x	x	—	—
C. F.	57	6	..	x	—	—	x	x	x	x
M. W. H.	35	3	..	x	—	—	x	—	—	—
G. C. D.	60	6	..	x	—	—	x	x	—	—
S. W. C.	52	7	..	x	x	—	—	x	—	x
F. C.	51	..	1	x	—	—	x	x	—	—
J. R. C.	65	5	..	—	x	—	x	x	—	x
E. P.	50	6	..	—	—	x	—	x	x	x

* Ulcerative keratitis, 6; iritis, 4; uveitis, 2; choroiditis, 2; iridocyclitis, 1.

† Neuritis, 15; muscular, 20; cardiac, 4.

Occasionally prostatic infection may be caused by influenza or some other acute infection. Gastrointestinal and gall-bladder infections occasionally seem to play a part. It is surprising how rarely it has any association whatever with infections in the facial sinuses. The writer has never seen a case wherein he could trace such an etiologic influence and von Lackum¹ has had much the same experience.

Pemberton² has ably brought out the thought that there must be an initial systemic factor that probably antedates the determination of all of these infective foci as well as sensitizes the individual to their toxins. Consequently, though the mind is prone to center only on these foci, it has become increasingly obvious that such a narrow view is seldom to the best interest of the patient. In other

words, though all of the foci but the prostatic one may be removed, the patient is rarely a solely urologic problem.

In a review of these patients a number of interesting and important points have presented themselves. Prominent among these has been the great need for a constant watch for other tooth-root infections. Approximately 39 per cent of the patients had such later foci. This is particularly important in view of the fact that it is common custom to attend to existing dental infections and then dismiss the matter from further consideration. Repeated experiences of this sort have caused the writer to lay down the rule that such patients should have a full set of dental Roentgen rays 3 months after the removal of any infected teeth and at 6-month periods for the succeeding 2 years. The number of expensive dental bridges that have had to be removed for some of these later infections would seem to urge the wisdom of delay in this regard in many cases.

One should not dismiss this phase of the subject without a word regarding the tonsils, for some patients cling tenaciously to them. And evidence has not been altogether wanting to suggest that physicians are not always correct when they pronounce tonsils normal. This is further suggested by the fact that a number of those whose speciality has to do with the tonsils have told the writer that often one cannot really tell whether or not a tonsil should be removed until he has it in his hand, which would arouse the suspicion that at times our *dicta* outrun our science.

From a urologic standpoint one can lay down some rather fixed rules regarding the association of the prostatic infection with these more distant foci as well as the patient's systemic symptoms. These might briefly be stated as follows:

1. The prostatic infection cannot be permanently cleared up so long as the causal foci remain.

2. If no improvement is seen in the prostatic secretion after 6 weeks of routine prostatic massage it is probable that there are some other distant foci.

3. If the prostatic infection clears up and then recurs there are other dental infections, providing the tonsils are out.

4. If there are no further dental infections and the prostatic infection recurs the diagnosis of normal tonsils in all probability is wrong.

5. If the distant foci in teeth or tonsils supposedly have been removed and the patient is not markedly improved after 6 weeks of prostatic treatment, one had better investigate the gall bladder or question the last Roentgen ray of the teeth and have it repeated.

6. If these are all negative, and there is no change in symptoms, he can be assured that the prostate has little, if anything, to do with the distant symptoms, and he would do well to center attention on the gastrointestinal tract.

Some years ago the writer called attention to the occurrence of

an increase in the distant symptoms following prostatic massage.³ In the most severe reactions of this type there was a chill, elevation of temperature and a marked increase in pain, if pain was a symptom of the ailment. In the milder reactions there was but a slight increase in the distant symptoms. The reactions generally occur within 12 hours of the digital manipulation of the gland, last perhaps 12 hours and are followed by a transient improvement beyond that previously existing. The occurrence of this reaction is at times delayed for 24 or 48 hours.

Regarding such reactions one again can lay down some rather fixed rules.

1. Their occurrence is proof that the prostate is a factor in the disease.

2. Their absence does not prove the innocence of the prostatic infection.

3. They occur in at least 50 per cent of the cases.

4. They correspond in every way with a protein or vaccine reaction with a specific affinity for the distant symptom-giving lesion.

5. Being of the nature of a vaccine reaction they urge the wisdom of viewing the prostatic manipulation from the standpoint of vaccine dosage and varying the pressure accordingly.

6. The procedure causing them should not be repeated until at least 3 days after they have subsided.

7. Too profound a reaction reduces the patient's curative response and if prostatic manipulation is too roughly or too often done they may do irreparable harm.

8. They are particularly dangerous in the presence of ocular inflammation.

9. They cause great pain and joint swelling in the presence of marked joint involvement and, if profound, delay cure for many weeks.

10. They rarely occur after more than the first few prostatic massages, but if they continue to follow even the gentlest massage the massage should be discontinued and every effort made to improve the general health before it is started again.

11. Prostatic massage should not be carried out within a week of tonsillectomy or tooth extraction if these have caused any increase of the distant focal infective symptoms.

12. The more acute the distant symptoms for which prostatic massage is carried out the gentler should be the massage. Particularly is this true of inflammations of the eye, wherein subsequent reactions are often severe and prolonged.

13. Except in the most severe cases, the pain of neuritis and arthritis is relieved or banished within four weeks of the institution of regular prostatic massage, providing the prostate is the only infective focus left.

In other places^{4,5} the writer has had much to say about the

diagnosis and treatment of prostatic infections, some of which might bear repeating in the present connection. To one who has had much experience with the focal infective prostate it is obvious that these infections differ somewhat from those that result from gonorrhea. In the latter all of the gland follicles become infected so that no normal prostatic secretion is present. Pus is everywhere in evidence in the microscopic field.

In the prostatic infections secondary to more distant foci the infective process often is not so general. In fact, it may be so deeply placed that one may on the first massage obtain only normal secretion, pus being evident only at a later study. So frequently is this the case that it is unwise to pronounce the prostate normal until a normal secretion has been obtained on at least two studies within 3 days of each other. If on the second study there is a quantity of granular débris or an excessive number of lecithin granules a third study should be made.

If digital manipulation of the gland causes any increase whatever in the distant symptoms one can feel assured that, though the obtained secretion be microscopically normal, there is infection present and that further treatment is essential. The occluded follicles soon will begin to drain and pus appear in the secretion. This is not the case with the normal gland. No prostate should be considered normal without microscopic study of its secretion. Palpation is a reliable guide only insofar as it may reveal the presence of tuberculosis, carcinoma or hypertrophy. Hard nodulation of the prostate usually means tuberculosis or carcinoma, for neither of which is massage good treatment.

The hypertrophied prostate is usually infected, and if massage is carried out it should be done with due regard to the possibility of hemorrhage. Pressure should be very carefully made upon the midline, if it is made at all, for such patients often have very thin-walled varicosities in the posterior urethra and at the vesical outlet and dangerous hemorrhage may follow even gentle digital disturbance of the gland.

Prostatic massage in patients known to have tuberculosis of the lung or elsewhere should not be carried out unless it is proved that the prostatic infection is causing distant lesions of such importance as to make it worthwhile to incur the occasional risk of precipitating massive or a miliary tuberculosis. If massage is carried out in such patients it should be continued only to the point of establishing better drainage and not necessarily cure of the local infection.

Massage should not be carried out more often than twice a week and, as has been pointed out, it should be done with the utmost respect for its possible harm. It should be withheld or discontinued just so soon as it does more harm than good. If there are no longer any distant infective foci, and the microscopic appearance of the secretion fails to make further improvement after several

months of treatment, it is advisable to discontinue treatment for 6 to 8 weeks and then start another course of treatments.

If the secretion becomes normal the patient should be restudied several times during the next year to make sure that cure is permanent. A relapse of infection urges the importance of a study for other possible foci in the teeth or elsewhere.⁶

Autogenous vaccines only have served to prolong the infection of those to whom they have been given in this series. This is readily understood when one considers that prostatic massage in these patients forces into the system variable quantities of bacterial toxin, as evidenced by the typical vaccine reaction so often resulting therefrom. This virtual autovaccine therapy must by the nature of things be followed by a negative phase, and one hardly would expect a high degree of immunity effort in an individual in whom every second negative phase was made greater by the administration of a large injection of the same toxin. Particularly should this be true with treatments placed at 3-day intervals.

Summary. 1. The male focal infective triad is teeth, tonsils and prostate gland.

2. Thirty-five per cent of males beyond the age of 35 years have infected prostate glands.

3. At least 72 per cent of males with focal infective symptoms have infected prostates.

4. The focal infective prostate has almost no relation to gonorrhea.

5. Sixty-one per cent of patients with infected prostates have infected teeth and 69 per cent or more have infected tonsils.

6. At least 64 per cent of those having teeth extracted for infection have later infections of other teeth.

7. Roentgen rays should be taken of the teeth in such patients at intervals for at least 2 years.

8. At least 50 per cent of those patients having prostatic infection associated with distant symptoms experience an increase of these symptoms following prostatic massage.

9. These increases in symptoms are analogous to a vaccine reaction and, if too profound, may destroy the patient's curative responses.

10. The pressure of massage must be viewed from the standpoint of vaccine dosage and varied according to the degree of reaction it produces.

11. Great care should be taken in the presence of iritis, ulcerative keratitis, choroiditis and myocarditis not to cause a dangerously severe reaction.

12. It may take several studies of the prostatic secretion in these patients before one is safe in saying the gland is not infected.

13. A distant reaction following massage is proof of infection of the gland and even in the absence of observable pus indicates further treatment.

14. The recurrence of a prostatic infection after cure is almost positive proof of other distant and causal infection.

15. Nodulation of the prostate gland usually means tuberculosis or carcinoma and massage should be withheld until both are proved to be absent.

16. The prostatic secretion should be restudied several times in the year following apparent cure.

17. Autogenous vaccines have proved decidedly disappointing in prostatic infections, seeming to favor chronicity rather than cure.

18. The focal infective picture usually comprises more than attention to the foci of infection alone. Back of it there usually is a patient needing careful medical attention.

REFERENCES.

1. Von Lackum, W. H.: J. Urol., 1927, 18, 293.
2. Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1929.
3. Pelouze, P. S.: Med. Rec., 1921, 100, 412.
4. Pelouze, P. S.: Med. Clin. North America, 1929, 12, 1019.
5. Pelouze, P. S.: Gonorrhea in the Male and Female, Philadelphia, W. B. Saunders Company, 1931.
6. Clark, A. L.: Med. Clin. North America, 1931, 14, 917.

"ASEXUALIZATION" OF THE PLASMODIUM IN INDUCED MALARIA.

BY NICHOLAS KOPELOFF, PH.D.,

RESEARCH ASSOCIATE IN BACTERIOLOGY.

N. BLACKMAN, B.S.,

AND

B. MCGINN, B.A.,

NEW YORK CITY.

(From the Department of Bacteriology, Psychiatric Institute and Hospital, New York.)

AN asexual strain of induced malaria¹ eliminates the possibility of further transmission by mosquitos and precludes the occurrence of malarial relapse after adequate quinin administration. Another practical advantage of such a strain is that screening and isolation of patients becomes a superfluous procedure. Consequently we have attempted to asexualize a sexual strain of benign tertian malaria by continuous human passage. In a previous report² of progress dealing with 123 patients it was stated that "after 7 months the sexual strain of malaria began to lose its capacity to produce gametocytes. During the succeeding 9 months this was found to be much more striking in female than in male patients."

At this time additional evidence may be brought forward. Obviously it was impracticable to examine daily smears from all the patients inoculated with malaria in all the New York State Hospitals. However, we did succeed in examining daily smears (Wright-stained) from at least one patient at every passage. Occasionally, when the strain ran out at one hospital, it was necessary to renew it from another. Hudson River State Hospital and the State Hospitals farther south used the so-called "Poughkeepsie strain" exclusively for the purpose of this experiment. The northern State Hospitals continued the "Institute strain" which has been through continuous human passage since 1923 and has always failed during the period of examination to show the presence of any sexual forms (gametocytes).

A word of explanation is relevant as to the microscopic criteria of differentiating sexual from nonsexual parasites in benign tertian malaria. Unless the plasmodium completely fills the red blood cell, it is extremely difficult to make a decision, consequently only fully grown gametocytes have been accurately identified. Further, the chromatin must be localized and not distributed. The question of mosquito infectivity has not been solved, first, because we have not been able to devote sufficient time to breeding mosquitoes in adequate numbers (the few we raised failed to survive) and second, there is always the doubt as to whether enough sexual forms are present to infect a mosquito. In other words, there might be a few sexual forms which failed to infect the mosquito, but such failure would not be a proof of asexuality. Therefore, we have preferred to base our differentiation on careful microscopic examination.

In addition to the 1700 smears from 123 patients previously reported we have since examined 1011 more of the "Poughkeepsie strain," making a total of over 2700, together with over 400 additional slides of the "Institute strain," or more than 3000 smears in all. Smears from 129 patients inoculated with the "Poughkeepsie strain" since August 8, 1929, showed the following distribution up to October 18, 1930; Five females out of 21 patients had gametocytes and 33 male patients out of 90, or roughly about one-third the entire group (omitting those who showed no parasites).

The most striking feature of our data is the fact that after October 18, 1930, *no* patient inoculated with the "Poughkeepsie strain" harbored any gametocytes. Thus the diminution in sexual forms of the parasite as noted in our previous report may be said to have reached its logical conclusion, which is the total absence of gametocytes demonstrable by microscopic methods. Thus the last patient at the Manhattan State Hospital to show gametocytes was inoculated October 17, 1930, and the last patient at Hudson River State Hospital showing gametocytes was inoculated October 2, 1930. This would indicate that the capacity to produce sexual forms died out in this strain at a given age, approximately $2\frac{1}{2}$ years.

In our first report, in 1928, on the "Institute strain" of malaria in use since June, 1923, it was stated that "it is conceivable that gametocytes have been formed at some time in the past, and that the strain has since lost its power to produce sexual forms." The reexamination of slides from patients inoculated with the "Institute strain" in 1925 failed to reveal the presence of gametocytes. In other words, after about 2 years of continuous human passage no sexual forms were found. The evidence cited above with regard to the asexualization of the "Poughkeepsie strain" would tend to confirm the hypothesis just quoted concerning the "Institute strain." A further examination of 400 smears from patients inoculated with the "Institute strain" failed to reveal any gametocytes.

It is of interest to follow the loss of capacity to produce sexual forms in the "Poughkeepsie strain." The data have been summarized in Table 1.

TABLE 1.—GAMETOCYTES IN BLOOD SLIDES OF MALARIA-TREATED PATIENTS.

	No. of cases.		Average per cent of slides with parasites showing gametocytes.		Actual number of cases showing no gametocytes.		Per cent patients showing no gametocytes.	
	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.
Group 1 (May 9, to Nov. 2, 1928)	44	14	69	73	0	0	0	0
Group 2 (Nov. 2, 1928 to Aug. 8, 1929)	45	21	16	38	13	1	29	5
Group 3 (Aug. 9, 1929 to Oct. 18, 1930)	11	55	16	16	6	22	55	40
Group 4 (Oct. 19, 1930 to Mar. 30, 1931)	10	35	0	0	10	35	100	100
Males to May 2, 1931								

In Table 1 it will be seen that in the first 6 months (Group 1) there was a slight decrease in the average percentage of slides with parasites showing gametocytes. In the succeeding 9 months (Group 2) the decrease was more marked, particularly in females. In the 14 months following (Group 3), the percentage had reached the same low level in both males and females (16 per cent). In the last 6 months no gametocytes were found in either males or females.

These results cover a total of 252 patients inoculated with a sexual strain of benign tertian malaria. The loss of capacity to produce sexual forms is clearly brought out in the last column of Table 1, where in both females and males 100 per cent absence of gametocytes is shown. This means that we have been dealing with a true instance of biologic adaptation. Sexual forms are necessary to perpetuate the malarial organism when it has to depend on mos-

quitoes for transmission. But when artificial inoculation replaces the mosquito, sexual forms become superfluous and disappear.

Summary. 1. The continuous human passage of a sexual strain of malaria inoculated into patients with general paralysis on August 8, 1929, has resulted in the complete absence of gametocytes on October 18, 1930. No sexual forms were found after this date.

2. Approximately $2\frac{1}{2}$ years were required to obtain a true biological adaptation of the malarial parasite. Since sexual forms are necessary for the transmission of malaria by mosquitoes, the method of artificial inoculation has rendered them superfluous.

The accumulation of daily smears from consecutive patients has been a difficult and painstaking task. Without the excellent coöperation of the superintendents of the New York State Hospitals and their staffs, the completion of this research would have been impossible. Particular thanks in this respect are due to Dr. C. O. Cheney, Director of the Psychiatric Institute, formerly superintendent of the Hudson River State Hospital, and Dr. I. J. Furman, superintendent of the Manhattan State Hospital.

REFERENCES.

1. Kopeloff, N., and Fiertz, Charles O.: The Clinical Significance of the Life Cycle of the Parasite in Induced Malaria, *AM. J. MED. SCI.*, 1928, **176**, 664.
2. Kopeloff, N.: Inoculation Malaria: Sexual and Asexual Strains, *AM. J. MED. SCI.*, 1930, **179**, 800.

REVIEWS.

TEXTBOOK OF HISTOLOGY. By EUGENE C. PIETTE, M.D. Pp. 466; 277 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$4.50.

THIS textbook is planned and written along the usual lines of current histologies. As the preface informs us, the figures are taken from various sources. This work will be found useful in certain classes, particularly in dental schools, and while there is nothing strikingly new in the book, it in no way deviates from accepted standards. W. A.

LEHRBUCH DER SPEZIELLEN PATHOLOGISCHEN ANATOMIE, VOL. I. By DR. EDUARD KAUFMANN, Ord. Professor der Allgemeinen Pathologie und Pathologischen Anatomie an der Universität Göttingen, Geheimer Medizinalrat. Pp. 990; 506 illustrations. Leipzig: Walter de Gruyter & Co., 1931. Price, Rm. 55.

EVEN with the monumental system of Henke and Lubarsch, now in its 12th volume, at their disposal, pathologists and advanced students have relied on Kaufmann's textbook of special pathology as a standard for more extended reading than is possible in one volume works. While Reimann's English translation has been a great convenience in this country, it cannot replace the original, so that this new edition after an interval of 9 years is doubly welcome. A scientific book, as well as its readers, is fortunate in being able to pass through 10 editions during the lifetime of its author. Professor Kaufmann, who retired in 1928, has been most industrious in bringing this edition up to date—volume one alone contains over 7500 new references and 68 of the 430 odd illustrations are new and have comprehensive legends. In passing, one regrets that the American literature is not more adequately represented, but presumably it has not been freely available in post-bellum Germany. Among the rewritten topics are angina pectoris, sedimentation rate, blood groups, allergy esophagospasm, eclampsia, endometriosis, as well as larger sections on pulmonary tuberculosis, thyroid and parathyroid, liver and bile passages and so on. Let us hope that the other volumes will soon follow. E. K.

THE COMMONER NERVOUS DISEASES. By FREDERICK J. NATTRASS, M.D. (DUNELM.), F.R.C.P. (LOND.), Assistant Physician, Royal Victoria Infirmary, Newcastle-upon-Tyne. Pp. 218; 15 illustrations. New York: Oxford University Press, 1931. Price, \$4.00.

THIS volume is designed for the general practitioner and for it he will be grateful, but it is not sufficiently comprehensive to meet all the needs of the medical student. Such terms as N.A.B., and G.P.I., should be written in full. Epilepsy has been given 18 pages and the psychoneuroses less than half that space—the reverse would be an improvement. General Care of Paraplegic Cases is an excellent chapter. Newer matter that is of practical

use is included such as support by means of adhesive strips in facial paralysis, vaccine treatment of disseminated sclerosis, alcoholic injection of nerve trunks or the Gasserian ganglion in migrainous neuralgia and other worthwhile therapeutic measures.

The author's effort to point out "the possibilities of treatment and to show that these depend generally upon early diagnosis based on appreciation of the significance of symptoms," is achieved. The generous use of cross-reference is helpful, there is a useful bibliography and a good index.

N. Y.

MEDICAL PSYCHOLOGY. Monograph Series No. 54. By WILLIAM A. WHITE, M.D. Pp. 141; 4 illustrations. Washington: Nervous and Mental Disease Publishing Company, 1931.

THE author pleads for the placement of psychology on the same basis as physiology in the medical curriculum. The intention is not for more intensive study of the neuroses and psychoses by the student, "but to orient him with regard to the mental factor as it is seen in disease generally and more particularly in disease of the body, that is, somatic disease." Some such need is great for does not the quack sometimes succeed, with his crude knowledge of psychology, where the regular practitioner has failed? It is unlikely that the medical course shall be lengthened, therefore, if medical psychology shall be accorded serious consideration, a number of other courses must yield a portion of their time, since physiology alone could not afford so much curtailment. The subject-matter is advanced in orderly fashion, with a number of chapters gracefully presented from the psycho-analytic viewpoint.

N. Y.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE, VOL. 9. TECHNICAL METHODS, GENERAL INDEX. By VARIOUS AUTHORS. Pp. 363; 86 illustrations. London: Medical Research Council, 1931. Obtainable in the United States at the British Library of Information, 5 East 45th St., New York. Price, 1/1/9; for the set 8/14/9.

THE ninth and last volume of this splendid system (for Reviews of other volumes see AM. J. MED. SCI., 1930, 179, 120, 121; 1931, 180, 718; 1931, 182, 121, 271) by 27 authors is devoted to selected branches of general bacteriologic technique. On account of the vast field, the methods are arbitrarily selected without any discussion of principles or relative merits. The chief topics covered are the microscopic demonstration of bacteria, culture media and pH, cultivation of anærobies and spirochetes, isolation of single cells, viruses, bacteriophage, biochemical and serologic methods, oxidation-reduction, production of variants, general handling of laboratory animals. A general index of 68 pages completes this valuable volume.

E. K.

PHYSICIANS' MANUAL OF BIRTH CONTROL. By ANTOINETTE F. KONIKOW. Pp. 233; illustrated. New York: Buchholz Publishing Company, 1931. Price, \$4.00.

THIS is a work that deserves wide circulation. The subject matter is well presented and the language clear, convincing, forceful; the arrangement good. It is really more than its modest title of "Manual" would infer. It is an excellent, but not too detailed, review of the whole subject of contraception, written from the practical viewpoint.

Part I deals with a general discussion of the urgent need of medically supervised contraception, exposes the absurdity of most of the current medical prejudices against it, and closes with a classification of all possible contraception methods.

Part II consists of a discussion, in order, of all the various methods employed, the author stating frankly her opinion of the merits and demerits of each.

Part III, in admirable detail, describes first the technique of the method the author prefers, then gives the reasons for the occasional failure, and lastly discusses the incalculable benefits of birth control from the psychic point of view.

Part IV is entirely statistical and, though of great interest, presents too small a series of cases to furnish material for dogmatic generalizations.

At the start of the book is a timely note for busy practitioners, telling them just where to turn for immediate practical information.

It is to be hoped that, through this book of Dr. Konikow's, the medical profession will avail itself of an opportunity for service to humanity hitherto rather neglected.

O. T.

How's YOUR BLOOD PRESSURE? By CLARENCE L. ANDREWS, M.D.,
Attending Physician and Medical Chief at the Atlantic City Hospital.
Pp. 225. New York: The Macmillan Company, 1931. Price, \$2.50.

ALONG with diet, vitamins, ultraviolet light and cancer, blood pressure has become a major topic of discussion among the laity. Because of numerous misconceptions regarding the workings of the circulatory system, many have become victims of a "blood pressure psychology" which has almost attained the proportions of a "blood pressure hysteria." In this book, written for the layman, the author attempts to allay many of the fears incident to all the misdirected talk about blood pressure. He presents the subject in a pleasing style and in language that can be understood by laymen. Many examples are drawn from well known physical principles to clarify the elementary presentation of the physiology of circulation. The book ought to satisfy, at least in part, the natural desire of the intelligent layman to know more about his own body.

A. C.

THE PHYSIOLOGY OF MUSCULAR EXERCISE. By the late F. A. BAINBRIDGE, M.A., M.D. (CANTAB.), D.Sc., F.R.C.P., F.R.S., Professor of Physiology, University of London. Rewritten by A. V. BOCK, M.D. (HARVARD), PH.D. (CAMBRIDGE), Assistant Professor of Medicine, Harvard; Physician, Massachusetts General Hospital, Boston and D. B. DILL, PH.D. (STANFORD), Assistant Professor of Biochemistry, Harvard. Pp. 272; 46 illustrations. Third Edition. New York: Longmans, Green & Co., 1931. Price, \$5.00.

THIS revision of Bainbridge's monograph provides many interesting data for those interested in this field, and is a perfect mine of information. Much new material has been incorporated without lengthening the book to any great extent. On the other hand the clear descriptive style of Bainbridge has been lost, and, though the general form of the book is unchanged, it can no longer be described as easy reading.

For instance in regard to physico-chemical changes in the blood, readers are referred to L. J. Henderson's Silliman lectures, and though graphs are given, no real attempt is made to summarize this subject in simple language.

The statement is made that "nothing takes place in the serum that does not have a fairly simple interpretation" but the reader would never guess it. In other parts similar difficulties are encountered, apparently due to the same determination to conserve space.

The material is admirably up to date, and almost the only criticism that can be made is that the revisers have failed to discard completely the larger values for circulation rate obtained by modified Haldane methods in favor of the lower values given by acetylene and by Starr and Gamble's modified ethyl iodid methods. Their interpretation fluctuates somewhat between the two standards; the normal resting value is assumed as 5 to 6 liters per minute (p. 66) but later in considering the complementary value of oxygen utilization lower values for circulation rate (3 to 4 liters per minute) are considered valid (p. 130).

H. B.

THE CONQUEST OF OLD AGE. By PETER SCHMIDT, M.D. Translated by EDEN and CEDAR PAUL. Pp. 307; 40 plates. New York: E. P. Dutton & Co., 1931. Price, \$5.00.

EVER since the appearance of Steinach's *Verjüngung* in 1920, many have looked upon the idea of rejuvenation with scorn because of its connection with a revival of sexual powers. Humorists, columnists and even critics among medical men took up the theme and reduced it to absurdity with the result that what was truly scientific in the work of the Viennese scientist met with little appreciation. The author of "The Conquest of Old Age," a disciple of Steinach, addresses his book to both physicians and laymen. With all the enthusiasm of the specialist, he presents the facts as he sees them in the hope that Steinach's work will receive more widespread recognition. All the case histories presented show strikingly good results, but no claim is made for 100 per cent successes. No statistics are given because of the incompleteness of follow-up data, yet the author states that his various rejuvenation operations have yielded a higher percentage of good results during the last 2 years than H. Benjamin's 77 per cent successes reported in 1926.

At times, the author carries his enthusiasm a bit too far. For example, in discussing rejuvenation and its critics, he says, "People shrink from the extra work involved in the learning of new theories and the mastering of new practical methods. The general practitioner, moreover, is afraid lest there may no longer be a field for the application of much of his therapeutic knowledge and skill if all the disabilities of old age can be shuffled out of the world." This argument is obviously rather weak.

The reader who is interested in the rejuvenation controversy will find enough facts in the book to decide for himself.

A. C.

A TEXTBOOK OF SURGERY. By JOHN HOMANS, M.D., Assistant Professor of Surgery, Harvard Medical School. Pp. 1195; 513 illustrations. Springfield, Illinois: Charles C Thomas, 1931. Price, \$9.00.

In a single large volume the author has attempted to present in textbook form, material which comprises the specialty of general surgery as taught at Harvard Medical College. Under "General Surgery" the author has grouped many of the branches of the so-called surgical specialties. Practically no operative technique is given. Though the substance has been furnished by a number of different individuals, yet the material has been condensed, correlated and apparently rewritten by the author-editor. This

results in a uniformity of presentation and style which is most commendable and worthy. It is only through the physical limitations of the book that it has failed to achieve its purpose of an authoritative text. Due to these limitations, much valuable material has been omitted. Undesirable curtailment has been resorted to. It cannot be said that the book is up to date, as in many instances the more recent advances of knowledge in various disease processes and forms of treatment are not mentioned. The book is printed on thin, light weight paper of poor quality, which creases and wrinkles easily. There are a number of line drawings, reproduced in black and white. These illustrations, due to lack of shading, are inartistic, though illustrative. In many instances, the illustrations remind one of the inferior woodcuts used in surgical texts of some 40 or more years ago. Though the book will probably enjoy a large sale because of the contributors, it will not challenge the supremacy of the texts of Da Costa, Ashhurst, or other present-day masters.

G. W.

CRIPPLED CHILDREN. THEIR TREATMENT AND ORTHOPEDIC NURSING. By EARL D. McBRIDE, B.S., M.D., F.A.C.S., Instructor in Orthopedic Surgery, University of Oklahoma, School of Medicine. Pp. 280; 159 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$3.50.

THIS small book is written for the purpose of imparting orthopedic information and instruction to the nurse, parent and the social worker having to do with the care of the crippled child. The author, in so limiting the scope of his book, has created an almost impossible task. It is to be regretted that he has failed in this self-imposed task. The text is too brief and rudimentary to serve as a textbook for nurses. On the other hand, the material is presented in a too didactic and inelastic technical manner to be of much service to the social worker or parent. The material is presented in an almost barren outline form. The author's opinions are set forth in the form of unchangeable dicta. No attempt is made to present the views of those who do not agree with the author. There are many excellent photographic illustrations, a few Roentgen rays, and an occasional line drawing. The illustrations alone save the book from being worthless. It is impossible to recommend this treatise to those whom the author has attempted to reach.

G. W.

SURGICAL PATHOLOGY OF PROSTATIC OBSTRUCTIONS. By ALEXANDER RANDALL, M.A., M.D., Professor of Urology, University of Pennsylvania. Pp. 266; 75 half-tones and 22 line engravings. Baltimore: Williams & Wilkins Company. Price, \$7.00.

"AN analysis of 1215 autopsies studying especially 4 lesions of importance: hypertrophy, median bar, carcinoma and abscess."

Randall presents here the gross morbid pathology of "prostatism" as seen in the largest series of postmortem examinations as yet collected. This monograph is the first thorough attempt to classify macroscopic alterations occurring in the prostate gland, while previous authors have confined their researches to the etiologic and microscopic factors involved. If Randall's classification is accepted, which it well may be, a uniformity of nomenclature regarding prostatic pathology is possible that would eliminate the conflicting diagnoses and titles that are employed at present. Much confusion has existed heretofore in the literature regarding the classi-

fication of prostatic obstruction, especially the condition known as "prostatic bar." The author clearly differentiates the glandular bars, which are really hypertrophies of the posterior commissural tissue from the fibrous bars, which latter may be inflammatory in origin.

The illustrations are unusual in their excellent photography showing each condition in true size, so that accurate comparisons may be made between individual cases. A number of typical examples of each pathologic aspect are shown. Statistics as to age, race and type are presented in considerable detail including graphic charts.

This publication is most opportune as a contemporary writer claims that the gross changes such as found by Randall at autopsy do not exist as pathologic entities. The conclusions of Randall seem quite definite when supported, as they are, by numerous actual specimens.

This book should prove of interest both to the specialist and practitioner who is interested in the problem of vesical outlet obstruction. Prostatism has been recognized generally as an important element in many cardio-renal and vascular conditions and in this publication may be found the factors for urinary retention and bladder dysfunction. Randall's work is an authoritative and scientific presentation of facts that have been greatly needed to clear a heretofore poorly understood pathologic picture.

The plan of this monograph does not necessitate indexing, but a detailed index would be of great aid in locating readily the subject matter. A more detailed bibliography would facilitate in locating original references.

F. S.

MEDICAL ELECTRICITY FOR STUDENTS. By A. R. I. BROWNE, Member of the Society of Radiographers, Radiographer at the Royal Alexandria Infirmary. Pp. 245; 88 illustrations. Third Edition. New York: Oxford University Press, 1931. Price, \$4.00.

THIS is an elementary textbook written, primarily, for physiotherapy technicians. In the text are discussed, briefly, various electrotherapeutic currents, their physical characteristics and mode of action as well as their methods of application and therapeutic indications. Various types of apparatus are also described and information given as to their construction and mode of employment. The static machine, however, is not mentioned and the chapter on high frequency and diathermy is entirely too brief to be of any value.

As a whole the little volume is capably written in a clear, comprehensible manner. It is a production that should be of considerable instructive value for beginners in the study of medical electricity.

J. N.

TRAUMATOTHERAPY. THE TREATMENT OF THE INJURED. By JOHN J. MOORHEAD, Professor of Surgery and Director, Department Traumatic Surgery, New York Post-Graduate Medical School and Hospital. Pp. 574; 625 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$7.00.

HEREIN is contained a wealth of experience in the treatment of acute injuries. Each page is filled with valuable, practical material, clearly and concisely presented by the outstanding expert in this specialty. The Reviewer is unacquainted with any textbook that compares with Professor Moorhead's most recent work. "Traumatotherapy" should be the *vade mecum* of every industrial surgeon and of those general practitioners who are called upon to render emergency first aid.

G. W.

A LIFE OF JOSEPH PRIESTLEY. By ANNE HOLT. With an Introduction by FRANCIS W. HIRST. Pp. 221; 1 illustration. New York: Oxford University Press, 1931. Price, \$3.50.

PRIESTLEY's fame as a scientist, especially in connection with the discovery of oxygen, rests secure and his scientific progress can easily be followed in Thorpe's *Life in the English Men of Science* series. His theological, historical and even political activities, however, with which he personally was more intensely concerned, have received but scant attention; "it was thus with the object of rescuing Priestley's many-sided life from oblivion that this study was undertaken." The task has been well and pleasantly accomplished. Not only does a clear impartial picture of the man himself emerge, but also his dogmatic but rationalistic theology is seen preparing the way for the Higher Criticism of the next century and his radical philosophy marked real progress in philosophic studies. The hostility that resulted in the destruction of his library and laboratory in Birmingham drive him in 1794 to the "sweet situation" and "delightful retreat" of Northumberland. This local color and the fact that his descendants still flourish in this country should add to his interest for Pennsylvanians. The exile enjoyed the friendship of Jefferson and many other intellectuals, while the American Philosophic Society went far to make up for the loss of the Royal Society at home. It is interesting to learn that he preferred the simplicity of his pioneer home to the professorship of chemistry at the University of Pennsylvania which he declined, though he was able frequently to cover the 130 odd miles to Philadelphia to preach religion and talk philosophy.

Three pages of Bibliography and Manuscript Sources increase the value of this work for Priestley's admirers, though it unfortunately is far from a complete list of the works from his pen.

E. K.

BOOKS RECEIVED.

NEW BOOKS.

Publications of the Committee on the Costs of Medical Care: No. 14. The Costs of Medicine. By C. RUFUS ROREM, PH.D., C.P.A., and ROBERT P. FISCHER, B.S., PHAR.D. Pp. 250. Price, \$2.50. *No. 16. The Healing Cults.* By LOUIS S. REED, PH.D. Pp. 134. Price, \$2.00. Chicago: The University of Chicago Press, 1932.

Roentgenologic Studies of Egyptian and Peruvian Mummies. Anthropology Memoirs, Vol. III. By ROY L. MOODIE, Paleopathologist to the Wellcome Historical Museum, London. Pp. 62; 76 plates in photogravure, chiefly from roentgenograms. Chicago: Field Museum of Natural History, 1931. Price, \$5.00.

The Expectant Mother's Handbook. By FREDERICK C. IRVING, A.B., M.D., Professor of Obstetrics, Harvard Medical School, etc. Pp. 203; 26 illustrations. New York: Houghton Mifflin Company, 1932. Price, \$1.75.

Cancer: Civilization: Degeneration. By JOHN COPE. Pp. 293; 55 illustrations. London: H. K. Lewis & Co., Ltd., 1932. Price, 15/- net.

Clinical Interpretation of Laboratory Reports. By ALBERT S. WELCH, A.B., M.D., Clinical Instructor in Medicine in the University of Kansas School of Medicine in Kansas City, Kansas, etc. Pp. 366; 16 illustrations, 1 in color. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$4.00.

Anaesthesia. By W. STANLEY SYKES, M.A., M.B. (CANTAB.), D.P.H. (LEEDS), M.R.C.S., Anesthetist to the General Infirmary at Leeds, etc. With a section on Local Anesthesia by P. J. MOIR, M.C., M.B. (GLASGOW), F.R.C.S. (ENG.), Hon. Assistant Surgeon, General Infirmary at Leeds, etc. Pp. 128; illustrated. New York: W. W. Norton & Co., Inc., n.d. Price, \$2.00.

California's Medical Story. By HENRY HARRIS, M.D., Associate Clinical Professor of Medicine, University of California; Chief of Medical Department, San Francisco Polyclinic. With an Introduction by CHARLES SINGER, M.D., D.LITT., University of London, London, England. Pp. 421; illustrated. San Francisco: J. W. Stacey, Inc., and Springfield, Illinois: Charles C Thomas, 1932. Price, \$7.00.

Practical Treatment of Skin Diseases. By EDUARD AHLSEDE, M.D., New York and Hamburg, Formerly Assistant Physician, University Skin Department, Direction of Professor Unna, Eppendorf Hospital, Hamburg, etc. Pp. 770; 77 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$12.00.

Human Cancer. By ARTHUR PURDY STOUT, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. Pp. 1007; 331 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

Resultats du Traitement Chirurgical de l'Angine de Poitrine. By D. DANIELOPOLU, Professeur de Clinique Médicale à l'Université de Bucarest, etc. Pp. 285. Bucarest, Roumania: Impr. Cultura, 1932.

A valuable summary by a pioneer in this method, including 54 observations on the method of suppressing the presser reflex and 82 observations on sympathectomy (stellate ganglion).

Cerebral Injury in New-born Children Consequent on Birth Trauma; with an Inquiry into the Normal and Pathological Anatomy of the Neuroglia. By ERIK RYDBERG. Pp. 247; 49 illustrations. Copenhagen: Levin & Munksgaard, 1932.

Builders of American Medicine. Being a Collection of Original Papers read before the Victor C. Vaughan Society of the University of Michigan Medical School. Pp. 243; illustrated. Ann Arbor: George Wahr, 1932.

English-speaking Students of Medicine at the University of Leyden. By R. W. INNES SMITH, M.D., (EDIN.) With Foreword by JOHN D. COMRIE, M.D., F.R.C.P., (EDIN.), Lecturer on the History of Medicine at the University of Edinburgh. Pp. 258; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price 16/- net.

Medical Men in the American Revolution, 1775-1783. The Army Medical Bull., No. 25. By LOUIS C. DUNCAN, Lieut.-Colonel, U. S. Army, Retired. Pp. 414; 53 illustrations. Carlisle Barracks, Pa.: Medical Field Service School, 1931.

Diseases of the Coronary Arteries (Myocarditis). By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University, etc., and HAROLD LUETH, PH.D., M.D., Formerly Instructor of Physiology, Northwestern University, Chicago. Pp. 164; 42 illustrations, 3 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, \$5.00.

Researches on Blackwater Fever in Southern Rhodesia. No. 6 of the Memoir Series of The London School of Hygiene and Tropical Medicine. By G. R. ROSS, M.B., CH.B., PH.D., D.P.H., Rhodesian Research Fellow, London School of Hygiene and Tropical Medicine. Pp. 262; illustrated with tables and charts. London: The London School of Hygiene and Tropical Medicine, 1932. Price, paper, 8s; cloth, 10s. 6d.

- Pain in the Pleura, Pericardium and Peritoneum.* By JOSEPH A. CAPPS, M.D., Professor of Clinical Medicine, University of Chicago, with the collaboration of GEORGE H. COLEMAN, M.D., Assistant Professor of Medicine, Rush Medical College. A Foreword by ANTON J. CARLSON, M.D., Ph.D., Chairman of the Department of Physiology, University of Chicago. Pp. 99; 33 illustrations. New York: The Macmillan Company, 1932. Price, \$3.00.
- The Heart Rate.* By ERNST P. BOAS, M.D., Associate Physician, Mt. Sinai Hospital, New York City, and ERNST F. GOLDSCHMIDT, Ph.D., Research Fellow (1930-1931), Department of Surgery in the Yale University School of Medicine. Pp. 166; illustrated with figures and charts. Springfield, Illinois: Charles C Thomas, 1932. Price, \$3.50.
- Medicine Among the American Indians.* Vol. VII of *Clio Medica*. By ERIC STONE, M.D. Pp. 139; 17 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.
- Recent Advances in Pathology.* By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to the Royal Free Hospital, and LAWRENCE P. GARROD, M.A., M.B., B.Ch. (CAMB.), M.R.C.P. (LOND.), Bacteriologist and Lecturer in Bacteriology, Late Demonstrator of Pathology, St. Bartholomew's Hospital. Pp. 392; 67 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$3.50.
- Zur Kenntnis des Einflusses der Graviditäten und des Ergosterins auf das Wachstum.* By VON ERIK AGDUHR, Upsala. Pp. 82; illustrated. Upsala: Almqvist & Wiksells Boktryckeri-A.-B., 1932.
- Robert Koch. I. Teil 1843-1882.* By BRUNO HEYMANN, A. O. Professor an der Universität zu Berlin. *Grosse Männer Studien zur Biologie des Genies.* Herausgegeben von Wilhelm Ostwald. Zwölfter Band. Pp. 353; illustrated. Leipzig: Akademische Verlagsgesellschaft m.b.H., 1932. Price, paper, 16 M; bound, 18 M.
- The Surgical Clinics of North America, Vol. 12, No. 3 (Lahey Clinic Number, June, 1932).* Pp. 299; 123 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, paper \$12.00; cloth, \$16.00.
- Electrosurgery.* By HOWARD A. KELLY, M.D., LL.D., F.A.C.S., Baltimore, and GRANT E. WARD, M.D., F.A.C.S., Baltimore. Pp. 305; 382 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$7.00.
- A Series of Original Dry-point Portraits of British Medical Scientists.* By A. WATSON TURNBULL, 21 Sheen Road, Richmond, Surrey, England. Price, £5.5.0 each.
- This is an attractive set of dry-point portraits of such famous British medical scientists as Lord Lister, Sir J. Y. Simpson, Sir James Paget, Sir Patrick Manson, Sir Arthur Keith, and Sir Ronald Ross. The edition is limited to 25 signed and numbered artist's proofs from each plate which is to be destroyed. The plates are 11 inches high by 9 inches wide, giving a head about 4 inches high.
- Minor Surgery of the Urinary Tract.* Mayo Clinic Monograph. By HERMON C. BUMPUS, JR., Ph.B., M.D., M.S. in Urology, F.A.C.S., Associate Professor of Urology, The Mayo Foundation. With a chapter on Carbuncles by JOHN L. CRENSHAW, M.D., Associate Professor of Urology, The Mayo Foundation, and chapter on Postoperative Care by ANSON L. CLARK, M.E., M.D., Section on Urology, The Mayo Clinic. Pp. 124; 57 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$3.00.

Collected Papers of The Mayo Clinic and The Mayo Foundation, Vol. XXIII, 1931, Published, May, 1932. Edited by MRS. MAUD H. MELLISH-WILSON and RICHARD M. HEWITT, B.A., M.A., M.D. Pp. 1231; 265 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$13.00.

The usual wide range of topics is covered in this fine volume of 191 articles by those on or connected with the Mayo staff. There are also included 124 papers by title and reference. Sub-sections are: Alimentary Tract; Genito-urinary Organs; Ductless Glands; Blood and Circulatory Organs; Skin and Syphilis; Head, Trunk and Extremities; Brain, Spinal Cord and Nerves; Technic; Miscellaneous.

NEW EDITIONS.

Lang's German-English Dictionary. Revised and Edited by MILTON K. MEYERS, M.D., Neurologist to the Northern Liberties Hospital; Chief of Nerve Clinic, St. Agnes Hospital; Consulting Neurologist, Jewish Hospital, Philadelphia, etc. Pp. 926. Fourth edition, enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1932. Price, \$10.00.

Just as a knowledge of German is essential to the proper study of medicine, so an excellent dictionary like this is essential both in helping with difficult passages and in giving exact meanings to difficult words. Much space could be saved by omitting the repetition on each page of 3 lines of pronunciation examples.

The Mongol in Our Midst. By F. G. CROOKSHANK, M.D., F.R.C.P. Pp. 539; illustrated. Third edition, greatly enlarged and entirely rewritten. London: Kegan Paul, Trench, Trubner & Co., Ltd., 1931. Price, 21s. net.

Special Cystology. By various contributors. Edited by EDMUND V. COWDRY, Washington University, St. Louis. Pp. 1838; illustrated. Second edition. Three volumes. New York: Paul B. Hoeber, Inc., 1932. Price, \$30.00.

A Text-book of General Physiology. By PHILIP H. MITCHELL, PH.D., Professor of Physiology at Brown University. Pp. 799; 196 illustrations. Second edition. New York: McGraw-Hill Book Company, Inc., 1932. Price, \$6.00.

As compared with the first edition (1923) "the second edition differs radically in that much less space has been given to the biochemical aspects of physiology in order to make room for more physical chemistry as applied to physiology. To this end several of the earlier chapters have been eliminated or condensed, and four entirely new ones, Surface Action, The Colloidal State, Diffusion and Osmosis, and The Permeability of Cells, have been added."

A Manual of Pharmacology. By TORALD SOLLMAN, M.D., Professor of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Pp. 1237. Fourth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, \$7.50.

The following sections have been largely rewritten: Arsphenamin fate—Barbiturates—Bismuth—Cinchophen toxicosis—Gold—Iodin compounds in roentgenography—Liver extract—Mercury—Morphin addiction; fate; peristalsis—Nitric vapors—Pituitary—Quinin and plasmoquin—Sexual hormones—Temperature regulation—Thallium—Vitamins. The main purpose of the book—to furnish an outline of the current conception of the actions of drugs—has been well maintained.

Materia Medica, Pharmacology, Therapeutics and Prescription Writing. By WALTER A. BASTEDO, PH.G., M.D., Sc.D. (HON. COLUMBIA), F.A.C.P. Pp. 739; 78 illustrations. Third edition reset. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.50.

"New articles have been added on suprarenal cortex, ephedrin, quinidin, plasmochin, yatren, ethylene, the barbiturates, pre-anesthetic narcotics, carbon dioxid, carbon tetrachlorid, the antiseptic dyes, mercurochrome, metaphen, the mercury diuretics, phenylhydrazine, insulin, ovarian preparations, colloidal lead in cancer."

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Relationship Between Liver Injury Induced by Alcohol and Elimination of Phenolsulphonaphthalein.—DEB. MACNIDER and DONNELLY (*Proc. Soc. Exper. Biol. and Med.*, 1932, 29, 586) mention that in previous communications they recorded a rather bizarre series of results obtained from the injection of phenolsulphonaphthalein in dogs poisoned by ethyl alcohol. In some of these animals there would be a reduction in the output of dye lasting throughout the course of experiments; in another group the dye eliminated would be only slightly affected, whereas in the third group an occasional animal developed albuminuria with casts and every symptom of nephritis, yet the elimination of the dye would rise 20 to 30 per cent. An explanation of these unusual results is suggested in some recent contributions from Whipple, *et al.* Dr. MacNider therefore investigated histologically the livers of animals intoxicated by alcohol in which there was considerable increase in the phthalein elimination in spite of the clinical evidence of nephritis. There was present marked liver injury involving first the periphery of the liver lobule and extending inward toward the central vein. This produced an extensive process with areas of degeneration showing marked cloudy swelling of the liver cells. The nuclei also showed a considerable accumulation of stainable lipoid material. The intertubular capillaries were distended with blood but no hemorrhage into the liver substances was observed, nor was there any increase in connective tissue. The control animals which showed diminished elimination of phthalein had not any of these characteristic changes in the liver lobules. These pathologic studies substantiated the hypothesis that in the presence of liver injury and renal disease the excretion of phthalein may be high as a result of decreasing the amount of dye excreted by the liver and intestines or else by a lowering of the ability of the liver to destroy the substance.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Intermittent Gastric Ileus Due to Mechanical Causes.—MEYER and SINGER (*Surg., Gynec. and Obst.*, 1931, 53, 742) say that a clinical syndrome consisting of pain in the upper abdomen, vomiting of gastric contents, distention of the stomach and pyloric obstruction as determined radiologically is referred to as gastric ileus. When caused by a mechanical condition which obstructs interruptedly, the designation intermittent gastric ileus of the mechanical type is applied. Personal experience has been had with four etiologic factors. The most important is the benign pedunculated gastric tumor which acts as a ball valve by prolapsing into the pyloric ring or which incites vigorous peristalsis, leading to intussusception of the stomach into the duodenum. A cauliflower carcinoma with a pedicle located just proximal to the pylorus illustrates the second type of mechanical cause of periodic obstruction to the gastric outlet. The third etiologic factor discussed is a gastrolith derived from powders used in the Sippy treatment for ulcer. A coëxisting pyloric stenosis prevented the passage of the concrement and occasioned intermittent impaction. The fourth and most unique type of cyclic obstruction was due to an anomalous redundant fold of prepyloric mucosa which, acting like an epiglottis, produced a discontinuous occlusion of the pylorus. Other mechanical causes of intermittent gastric ileus might be added to the ones illustrated and discussed. The object of the publication primarily is to direct attention to a clinical syndrome which permits recognition of hitherto obscure conditions that lend themselves admirably to surgical cure.

Bacterial Synergism in Disease Processes.—MELENY (*Ann. Surg.*, 1931, 94, 961) believes that certain bacteria have a synergistic function in the production of certain types of disease or symptoms of disease. This synergistic action should always be kept in mind in studying disease processes involving tissues, organs or systems in which mixtures of organisms are frequently or occasionally found. The author has made observation of the hemolytic synergism of two organisms found in the exudate in a case of chronic empyema; of the lethal effect in experimental animals of a mixed culture of organisms found in unsterile catgut which could not be produced by the same organisms in pure culture; of the adjuvant action of organisms found in cases of peritonitis demonstrated by the production of death with small fractions of minimal lethal doses of these organisms when injected together; of the almost exact duplication of bacteriologic findings in 2 cases of progressive gangrene of the abdominal wall following the drainage of a peritoneal abscess. These cases both yielded a micro-aërophilic streptococcus and a *Staphylococcus aureus* capable of producing a gangrene of the skin and subcutaneous tissues when injected together into experimental animals, while the pure cultures failed to produce the lesion.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Diet as a Prophylactic Agent Against Puerperal Sepsis.—If vitamin A has any therapeutic effect in septicemia, its value as a prophylactic agent should be even greater. Experimental work on young animals has suggested that vitamin A and carotene act as "anti-infectives" because if they are absent from or deficient in the diet, multiple foci of infection develop. The preventive and curative effects of vitamin A and carotene in the autogenous sepsis of the animals were equally great. GREEN, PINDAR, DAVIS and MELLANBY (*Brit. Med. J.*, 1931, p. 595) now report a study of the prophylactic action of vitamin A against puerperal sepsis in women. Substances essential for the growth of the embryo are obtained either from the food or from the body of the mother. The body, particularly the liver, can store considerable amounts of the vitamin A obtained from food. A depletion of this stored vitamin may well occur in certain cases of pregnancy. The reported study comprises 275 women treated with the vitamin preparation and 275 alternate cases which served as controls. All cases were delivered in the hospital. The women were instructed to take the preparation 1 month previous to the calculated day of labor. The preparation "radiostoleum" which was used contained vitamins A and D dissolved in a neutral oil; 1 cc. containing 150 "blue units (Carr and Price)" of vitamin A and 5000 units of vitamin D in the form of irradiated ergosterol. The women took one-half a teaspoonful of the preparation. In the group which took the vitamin preparation, there were only 3 cases of puerperal sepsis (1.09 per cent); in the control group there were 13 morbid cases (4.73 per cent). This difference was twice the standard error. The morbidity rate for the two groups combined was much lower than that of previous years. The total number of cases with pyrexia was 56 in the vitamin group and 98 in the control group. The difference is almost four times the standard error. The degree and duration of pyrexia was also greater in the control group than in the vitamin group. Twenty-six cases in the vitamin group and 27 in the control group were subjected to manual or instrumental intervention of a major kind. None of the vitamin group developed local infection, but 6 of the control group did. The authors believe that these results indicate that the administration of vitamin A during the last month of pregnancy diminishes the liability to a morbid puerperium. On experimental grounds, the authors claim that vitamin D possesses

little anti-infective action. Antenatal care should always include a diet rich in natural sources of vitamin A. Milk, egg yolk, green vegetables, carrots and butter should be taken unsparingly. Mammalian liver is also an excellent source of vitamin A. A well-varied natural diet of this kind also supplies adequate amounts of the vitamins B, C and D and the calcium, phosphorus, iron, copper, manganese and iodine essential for the pregnant women. If the diet has to be supplemented, cod-liver oil is the cheapest source of vitamins.

The Effectiveness of Follicular Hormones Administered Orally.—The majority of hormones of internal secretion are ineffective, or only slightly effective, when given orally as compared with parenteral administration. So far as the follicular hormone is concerned, the ratio of effectiveness between parenteral and oral administration varies, according to the literature, from 1 to 2.5 (Dohrn) to 1 to 100 (Laqueur). Furthermore, Allen and Doisy deny the effectiveness of this hormone on oral administration. Such a wide discrepancy may be the result of different methods of standardization or preparation of the hormone. SCHOELLER, DOHRN and HOHLWEG (*Wien Arch. f. inn. Med.*, 1931, 21, 323) have now reinvestigated this problem using preparations of varying physiologic potency. The preparations were administered orally to castrated female rats in a watery solution of 1.2 cc. volume. The results clearly indicate that the purer the preparation, the larger the amount required to induce estrus in animals. Thus relatively the largest amount of the crystallized hormone was required to produce estrus. The authors conclude that certain impurities accompanying the pure hormone probably increase absorption or protect the hormones from the action of other substances. Another series of experiments indicates that the same amount of follicular hormone is more effective if administered in several divided doses.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Symptoms in Congenital Lesions of the Heart that Permit Venous Shunting.—LEECH (*Am. J. Dis. Child.*, 1932, 43, 1086) studied 62 patients with congenital heart disease, found at postmortem, of such a nature as to permit venous shunting. He attempted to determine the presence or absence of characteristic symptoms and signs. Nearly half of these patients presented no clinical abnormalities referable to the circulatory apparatus. While the incidence of cyanosis, periodic as well as constant, was found to be somewhat higher in this group than among 20 other patients whose autopsies revealed congenital defects of the heart that did not permit of venous shunting, this sign was found not to differentiate sufficiently the two general types of lesions. Eight, or about 13 per cent, of the large group presented a syndrome

that was almost totally absent in the smaller group with the nonvenous shunt type of defect. In the larger group, 5 additional patients presented convulsive seizures not accompanied by cyanosis and respiratory distress. When other causes, such as pneumonia, epilepsy, meningitis and severely toxic conditions, can be ruled out and when the patient is known to have congenital heart disease, the occurrence of convulsive-like seizures, often epileptiform in character, sometimes followed by drowsiness and frequently accompanied by hyperpnea, may justly be interpreted as an indication of a lesion, or a combination of lesions, that permits venous shunting, especially if the patient shows a constant cyanosis, no matter how slight, or if the attack is accompanied by deep cyanosis.

Infantile Diarrhea.—POOLE, COOLEY and ELLWART (*Am. J. Dis. Child.*, 1932, 43, 1101) found that infants in whom acute diarrhea developed late in the summer showed an intoxication after a variable length of time when improperly or inadequately treated. The intoxication is the result of several factors—anhydremia, acidosis and bacterial toxins, the last occurring particularly when the intestinal tract has been invaded by such organisms as the bacillus of dysentery or streptococci. Patients with such a condition require prompt and energetic treatment in order to save their lives. During this critical period their chief requirement is water. They feel that each patient should be individualized. It is recommended whenever it is possible to avoid hospitalization after the most acute period is passed in order to avoid the virulent bacteria that may be present in a hospital ward. Unsweetened evaporated milk, diluted to one-half or two-thirds strength, with protein or carbohydrate additions, proved to be a satisfactory formula for most of the patients in this series as soon as they were able to take milk. A certain amount of discretion must be used in each case because of the degrees of variation found in the hydrogen ion concentration of the stomach contents and in the individual child's reaction to food. The evaporated milk formulas can be readily adjusted in percentage acidity and consistency to meet these special requirements.

The Incidence of Respiratory Infections During the First 5 Years of Life.—MCLEAN (*Arch. Pediat.*, 1932, 49, 279) made an intensive study of 1408 respiratory infections seen in 156 children in an attempt to find evidence of a periodic recurrent disease. A small number of children were included in this study so that all the patients were in intimate contact with the observer and were seen in practically all of their illnesses. A comparison of the average number of respiratory infections per patient and the average number of months per infection in the children with various groupings of the same age and length of observation, showed a marked consistency. During an exact period of 4 years from the date of birth in 86 and 70 children, 692 and 563 respiratory infections were seen. The average number of days between infections in the two series were 181.4 and 181.5 days. The average number of respiratory infections per patient in each series was 8.04 infections. The percentage of mild and severe infections in the two series was the same, 41 per cent mild and 59 per cent severe. Eight hundred and

forty-five respiratory infections were seen in 86 children observed for an exact period of 5 years from the date of birth. The children were placed in two groups of 43 patients. One group had 416 infections and the other 429, a difference of only 13 infections. In 70 children observed for an exact period of 4 years from birth 563 infections were seen. The patients were placed in two groups of 35 each. One group had 285 infections and the other 278, a difference of only 8 infections. In 140 children observed for an exact period of 4 years from date of birth, 1125 infections were seen. When the patients were placed in two groups of 70 children each, one group had 563 infections and the other 562 infections, a difference of only 1 infection. The monthly seasonal incidence of occurrences in 845 respiratory infections seen in 86 children observed for an exact period of 5 years from date of birth, compared with 563 respiratory infections seen in 70 children over an exact period of 4 years from birth, showed a definite consistency. Removal of tonsils and adenoids apparently had very little effect on either the number of or severity of respiratory infections. The consistency in the sameness of the total number of respiratory infections seen in various groupings of the same age, number and length of observations showed evidence of a periodic recurrent disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

The Treatment of Neurosyphilis.—SOLOMON (*Urol. and Cutan. Rev.*, 1932, 36, 223) summarizes his experience in the therapeutic management of three types of neurosyphilis, namely, paresis, tabes and cases with predominantly meningeal symptoms. In paresis eminently satisfactory results are obtainable in approximately 30 per cent of cases, either with tryparsamid or fever therapy alone, but the author believes that the most satisfactory results are obtained by a combination of these two methods. It seems logical to begin with the simpler method, namely, tryparsamid; but, if after 2 or 3 months, progress is slow or unsatisfactory, a change to fever therapy is indicated. Conversely, the patient given a course of fever at the outset of treatment should be continued on tryparsamid to the point of complete serologic cure. The author believes that malaria is the most effective type of fever therapy and typhoid vaccine the least effective. Diathermy would seem to be equally as effective as malaria. In tabes tryparsamid would seem to offer the best means of treating the majority of cases. Intraspinal therapy as well as fever therapy are sometimes of spectacular benefit in cases nonresponsive to tryparsamid. The latter drug at times, supple-

mented with arsphenamin and bismuth, produces serologic negativity and symptomatic relief in the vast majority of cases. The time required for serologic cure, however, varies from months to years. Some patients show progression in their disease despite any type of treatment now in use. In the meningeal type of neurosyphilis the author again highly recommends the use of tryparsamid, which is said to act almost, if not entirely, as a specific drug. Clinical improvement is usually prompt and serologic cure occurs within the first year. There are some cases, however, that take very prolonged treatment to obtain serologic reversal to negative. The author has had no personal experience with fever therapy in this phase of neurosyphilis, but is led to believe by logic as well as the experience of others that it would be effective. In summarizing, the writer pleads for a more intensive study of the syphilitic patient from the standpoint of spinal fluid findings, for when changes characteristic of central nervous system invasion occur in the spinal fluid, the effect of treatment on the spinal fluid formula must be given first place in the subsequent treatment of the patient.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Rare Ovarian Tumors.—The pathology of three rare ovarian tumors has been presented by MEYER (*Am. J. Obst. and Gynec.*, 1931, 22, 697) of Berlin in an interesting paper read before the American Gynecological Society. The first type of tumor he has called "disgerminoma," although it is often called "seminoma ovarii" because of its histologic similarity to the so-called seminoma of the testis. It is carcinomatoid in character since it consists of large epithelial cells. He has seen 27 cases of this type and has observed that these neoplasms are seen very often in pseudohermaphroditic individuals, but they are also seen in women with typically female bodies. The external genitalia and uterus are apt to be infantile in character, while in men such tumors are apt to be associated with cryptorchidism and poorly developed testicles. One of the striking features of this type of neoplasm is the early age of appearance, usually in the second or third decade. The author believes that they arise from an undifferentiated form of germinal cells which have lost their faculty of becoming either masculine or feminine in type and therefore can develop into identical pathologic structures in both types of sex glands. As these tumors originate from undifferentiated sex cells they necessarily will be void of any specific hormonal influence and thus fail to exert a specific stimulation for development of the secondary sex characteristics. They neither masculinize nor feminize the individual. They may attain enormous size and thereby

destroy the ovary and even the uterus, but if operated upon, the prognosis is good. The second type of tumor discussed is the granulosa cell tumor which may occur as a folliculoma, often associated with cysts; as solid masses or in thin cords or tubules; or as a diffuse structure resembling sarcoma. He believes that these tumors arise from undifferentiated cells and not from epithelial cells of the true follicle. They occur most frequently in women over 60 years of age in whom the ovary no longer contains follicles, so that it is impossible to think of their origin from follicle cells. Of 33 cases of this type studied by the author 1 died soon after the operation and only 3 from later metastases, 19 remaining permanently cured for varying periods of time ranging from 1 to over 4 years. In 27 of the cases bleeding was an important symptom. The endometrium was found frequently to be hyperplastic and the uterus enlarged. After removal of the tumor abnormal bleeding stopped and, in younger individuals, if not all the ovarian tissue was removed menstruation again became normal. He concludes that hypertrophy of the uterus was caused by the ovarian neoplasm, especially in those patients past the menopause. The third type of tumor presented is the arrhenoblastoma, which tends to cause women previously exhibiting normal female characteristics to take on those typical for the male sex. In these patients there is falling of the hair, deposits of fat, atrophy of the breasts, shrinkage of the opposite ovary and atrophy of the uterus with consequent amenorrhea and sterility. At the same time positive signs of masculinization appear such as male hirsuties, growth of a beard, enlargement of the clitoris and hypertrophy of the larynx with the development of a male voice. After removal of such a tumor the woman returns more or less fully to her former femininity, menstruation reappears and even pregnancy may occur. On the other hand, the signs of masculinity return with a recurrence of the growth. He believes that these tumors originate from undifferentiated germ cells which are not utilized during embryonic development but retain their sexual potency and proliferate later in life, exerting their influence in the direction toward masculinity. Patients afflicted with any of these three rare tumors are cured by operation in most instances without removal of the opposite ovary if it is unaffected.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

Concerning Certain Aspects of the Fundus of the Eye in Arterial Hypertension.—BAILLART (*Bull. de la Soc. d'Ophthalmologie de Paris*, October 18, 1930) thinks that in the main, patients with hypertension, even if they have retinal lesions, have good vision unless the macula

is affected. Even before the retina is visibly affected, they may complain of a transparent haze, black or luminous spots or balls of fire before the eyes; and they may have transient spells of loss of vision due to vascular spasms in the retina or in the occipital lobe. In patients with such symptoms, the retinal arterial pressure will be found to be elevated. The onset of retinal lesions in a patient with hypertension indicates a failure of compensation on the part of the kidneys, the viscera, or the vessels. Extensive retinitis, with edema of the disks, hemorrhages and fibrinous exudates, can occur in hypertensive disease while the kidneys are still normal and while the retinal vessels are anatomically normal. It is difficult to differentiate ophthalmoscopically the retinitis of hypertension from the retinitis of nephritis. Punctate exudates are usually present in the peripapillary region in the retinitis of nephritis, and usually absent in the retinitis of hypertension. In the retinitis of nephritis, as pointed out by Abrami, Gallois, and Sthelin, the retinal arterial blood pressure rises disproportionately to the general systemic blood pressure. These authors think that this relative increase of blood pressure in the retina indicates a more severe type of hypertensive disease with greater liability to renal complications and that it is associated with increased intracranial pressure. It is true that the retinitis of nephritis can be improved in some cases by spinal puncture. In 12 cases in which the ratio of retinal to general blood pressure was normal (45 to 100), the urea in the blood was essentially normal. In 8 cases in which this ratio was increased (75 to 100), the blood urea percentage was definitely elevated. Apparently, the relative rise of retinal arterial pressure is more marked in cases of hypertension with impaired kidney function, and is thus of diagnostic and prognostic importance. An increase in the ratio of retinal to general arterial pressure may be caused by inflammation, by increased intracranial or by a local vascular lesion in the retina. Increased intracranial pressure is present in certain cases of hypertension and may lead to the erroneous diagnosis of brain tumor. If the central artery of the retina is obliterated by anatomic lesions or by spasm above the level of the papilla, the retinal blood pressure will be relatively low. If the obliterative process involves the vessels or capillary bed peripheral to the artery examined, the blood pressure will be relatively increased. Such lesions in the small arteries are frequent in hypertension and give rise, through ischemia, to the advanced forms of albuminuric retinitis. The elevation of local blood pressure in the retina is then not always a sign of increased intracranial pressure. Its serious prognostic significance rests rather upon the severe vascular disease that it indicates. Baillart concludes that the appearance of retinal lesions in arterial hypertension is the sign of a serious involvement. The purely hypertensive retinitis and the so-called albuminuric retinitis are quite similar, the latter differing only in the fact that the extravasation into the retina is serum made toxic by renal insufficiency.

Fundus Manifestations in Metabolic Diseases.—CAMPBELL (*Canad. Med. Assn. J.*, 1929, 21, 530) finds that patchy contraction of the blood column is an indication of internal sclerosis. Widening and burnished-copper appearance of the central light streak occurs in medial sclerosis.

With these signs of sclerosis are associated changes at the arteriovenous crossings. Superficial, flame-shaped hemorrhages may be seen if hypertension accompanies the sclerosis. Sometimes round, punctate hemorrhages are found. Sclerosis of the vessels of the choroid may also be associated. In diabetes, retinitis never occurs in the young and is apparently related to the duration rather than to the severity of the disease. The changes may vary from fine, rounded, yellowish-white, solid masses around the macula to a picture resembling the retinitis of nephritis. The earlier lesions are susceptible to insulin and dietetic treatment. The more severe lesions are not improved by insulin though they do not contraindicate its use. Lipemia retinalis, on the other hand, is seen only in young diabetics in acidosis or coma. It clears up rapidly under insulin therapy. Nephrosis shows no fundus lesions. In septic focal nephritis, a few white areas of degeneration and hemorrhages, usually with a white center, may be seen. In about 10 per cent of cases of acute glomerulonephritis papilledema, cotton-wool exudates and hemorrhages occur. In the subchronic stage of parenchymatous nephritis, if the blood pressure is unusually high, hemorrhages and edema of the retina and disk may appear. The fundus changes in the nephritis of pregnancy resemble those seen in acute glomerulonephritis but are usually more extensive. The grade of edema may be great enough to cause detachment of the retina. Reattachment may occur; but further degenerative changes may seriously reduce vision. Early fundus changes are favorably influenced by therapeutic abortion; the late are not. In about 70 per cent, renal injury, and perhaps eye changes, will recur in subsequent pregnancies. In chronic glomerulonephritis, the retinitis is characterized especially by snow-bank exudates, hemorrhages, macular star, and anemia. Advanced renal insufficiency is present and is essential to the development of the retinitis. Death occurs within 1 or 2 years. Retinal vascular sclerosis is present before the onset of the retinitis and advances rapidly in its presence. The retinitis of malignant hypertension is characterized by hyperemia and edema of the disks, cotton-wool patches, and a fine macular star in the presence of marked contraction of the arteries and arteriosclerosis, usually not of the intimal type. This type of retinitis indicates a widespread vascular lesion and the life expectancy of these patients is short even if the renal function is satisfactory. Few other metabolic diseases show characteristic fundus changes. The spontaneous arterial pulsation seen in hyperthyroidism is an interesting exception.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

The Physiology of Drainage of Nasal Mucus. I. The Flow of the Mucous Currents Through the Drainage System of the Nasal Mucosa and Its Relation to Ciliary Activity.—The basic and ancillary sciences of medicine are not equal, nor is their rank of importance fixed. Con-

trariwise, like everything in Nature, their relative position in the scale is in a flux that is determined chiefly by the current demands of the march of Progress. While it is true, as HILDING (*Arch. Otolaryngol.*, 1932, 15, 92) says, that "rhinologists seem to have neglected the subject" (nasal ciliary activity and mucinous secretion), it is also true that otorhinolaryngology's renaissance challenges in fervor and scope that of any other departmental branch of medical practice and science. Long since have the laboratories for physiology, pharmacology, chemistry, pathology and bacteriology supplanted the dissecting room and the tool-maker's shop as the training ground in otolaryngology. This is as it should be. The author's report is based on a study of the flow of nasal secretion in 31 persons, on various portions of whose Schneiderian membrane dots of India ink were placed. No ciliary activity could be demonstrated in the anterior third of the nose, which drains largely through the inferior and middle meatuses. The mucosa posterior to this region exhibited active ciliary motion especially in those areas least exposed to the flow of the inspired air. Furthermore, the protective layer of mucus covering all intranasal surfaces is continuous with that in the pharynx and esophagus, and moves in a manner not unlike an intact membrane, being motivated by ciliary movement and traction. In its posterior two-thirds the nose may be said to have a new lining about six times an hour; and approximately once an hour in its anterior one-third. Drainage from the anterior inactive areas required an hour or more, in contrast to from 3 to 10 minutes in the posterior, active areas. Generally speaking, the course of ciliary movement is toward the nasopharynx.

Infections of the Throat Due to Hemolytic Streptococci and Their Relation to Arthritis and Arthralgia. I. Observations With Particular Reference to Streptococcus Epidemicus of Septic Sore Throat.—Purposing "to bring forth the importance of hemolytic streptococci from infections of the throat in certain arthritic manifestations and to emphasize the possible rôle of hypersensitiveness to these organisms." PILOT (*Arch. Otolaryngol.*, 1932, 15, 71) refers to former personal findings indicating that in routine cultures hemolytic streptococci occur in the throats of 61 per cent of persons and almost 97 per cent of excised tonsils; whereas *Streptococcus epidemicus* was found in the throat in less than 1 per cent (4 of 500 persons); and 3 of the 4 carriers of these streptococci had arthritic symptoms; and from the excised tonsils in 13.8 per cent (70 of the 506 pairs of tonsils) in 23 of which arthritis or arthritic pains were cited as the cause for removal, in addition to a history of sore throats. The author states that (1) arthritis and arthralgia may complicate scarlet fever, erysipelas, wound infections and sore throat due to hemolytic streptococci (2); that the development of the arthritis 3 or more weeks after the onset of the streptococcic infection suggests hypersensitiveness as an important factor; (3) that *Streptococcus epidemicus* of septic sore throat may be responsible for a relatively small number of cases of the rheumatic arthritis; (4) that the persistence of *Streptococcus epidemicus* is often associated with arthritis; and, finally, that tonsillectomy terminates the carrier state, and the associated arthritis frequently disappears.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

The Roentgen Ray in the Diagnosis and Prognosis of Upper Urinary Tract Infection.—In the roentgenologic study of the kidney. PLAGGEMEYER and WELTMAN (*Radiology*, 1932, 18, 23) regard roentgenoscopic pyelography as essential. By this method overfilling of the pelvis and consequent pain to the patient can be avoided. Obscure details can be studied better than in the pyelograms. Under vision the kidney can be palpated and its mobility and the relation of calculi, tumors, etc., can be noted.

Air and Gas in the Soft Tissues.—Air and oxygen in the soft tissues occur in connection with compound fractures, gunshot injuries, lacerated wounds, surgical emphysema and after local treatment with hydrogen peroxid. Gas bacillus infection occasionally complicates injuries and accidents. RHINEHART (*Radiology*, 1931, 17, 1158) holds that the earliest positive diagnostic finding is the demonstration on roentgenograms of the shadow defects produced by the gas. If made within 10 days of the accident every film of an injury in which the skin is damaged or broken, including the open reduction of fractures, should be carefully examined for evidences of gas. The conclusions from Roentgen ray examination are also of importance in selecting and directing the treatment of gas infections.

The Hilus of the Lung in the Child.—The roentgenologic diagnosis of tuberculosis of the bronchial glands is not made as often as it should, especially in children, according to ALTSCHUL (*Radiology*, 1931, 17, 1147). A hilus showing increased density, whether homogeneous or mottled, is always suspicious. Inequality of the hilar shadows is decisive for the diagnosis. In the majority of cases any enlargement of the glands is due to tuberculosis. In cases that are not recent a primary focus in the lung can usually be demonstrated. If a primary focus cannot be demonstrated one should recall that other infectious processes may give rise to glandular enlargement.

Influence of Ultraviolet Rays on Pharmacologic Potency of Digitalis.—Tincture of digitalis was irradiated with mercury vapor quartz lamps, with Roentgen rays and with radium by MACHT (*Arch. Phys. Therap., X-ray and Rad.*, 1932, 13, 5). Irradiation with ultraviolet rays for short periods of time produced a deterioration or weakening in the pharmacologic potency of the tincture, as tested on living plants and animals. On progressive and prolonged exposure to ultraviolet rays, a point was reached where the photochemical changes resulted in the

formation of products exhibiting a greater toxicity for both plants and animals. This stage, on still further exposure, was followed by a secondary weakening in the pharmacologic potency of the irradiated tincture. The shorter ultraviolet rays, particularly those transmitted through a chlorin-bromin gas filter, were more effective than the longer rays in producing the changes described above. Exposure to Roentgen rays, to radium and to radium emanations resulted in a product which was greatly reduced in its activity for the animal heart, on the one hand, but was greatly increased in toxicity for living plant protoplasm on the other.

The Effect of Ultraviolet Energy on Erythrocytes in Vitro.—Investigations carried out by MAYER and DWORSKI (*Arch. Phys. Therap., X-ray and Rad.*, 1931, 12, 709) showed that ultraviolet energy from a Kromayer lamp causes hemolysis of red blood cells. Liberation of pigment from human and guinea pig erythrocytes was accomplished without apparent rupture of the cells. The cytoplasm of the frog's red blood cells disintegrated completely, while the nucleus showed coagulative changes. In the experiments the wave lengths below 300 were responsible for the hemolysis.

Peptic Ulcer of the Esophagus.—A case of peptic ulcer at the lower end of the esophagus is reported by AURELIUS (*Am. J. Roentgenol. and Rad. Therap.*, 1931, 26, 696). Roentgenologically the ulcer was manifested as a small barium-filled niche. Aurelius considers peptic ulcer of the esophagus a definite disease and of sufficiently frequent occurrence to be of real interest and importance. It has as its cardinal symptoms pain, dysphagia, nausea and vomiting and occasionally hemorrhage and perforation. It has been infrequently diagnosed in the past, but with the development of facilities for Roentgen examination and esophagoscopy, and if sought for in cases of substernal or epigastric pain, its incidence will probably be higher than heretofore. The diagnostic criteria are as yet incomplete and the roentgenologist has an important duty to perform in their further development.

A Review of Pneumoconiosis.—In a comprehensive article of 58 pages the subject of pneumoconiosis is reviewed from the standpoint of its etiology, its pathology and its roentgenologic appearances by PANCOAST and PENDERGRASS (*Am. Jour. Roentgenol. and Rad. Ther.*, 1931, 27, 556). With respect to its etiology the writers again emphasize the overwhelming importance of silica. It is generally conceded that organic dusts either do not produce pneumoconiosis or their effect is so slight as to be disregarded. Coal is not included among the organic dusts. Workers in coal, asbestos, hard rock (mining, drilling), sand (pulverizing, sandblasting), granite, slate, iron ore, cement and vitreous enamel (painting) are among those liable to pneumoconiosis in varying degrees. The roentgenologic manifestations also vary somewhat with different dusts. In general the basic roentgenologic characteristics of the three stages of the disease as observed in this country are: First stage: A definite increase in the prominence and extent of the hilum shadows, an increased prominence and thickening of the trunk shadows,

and a greater prominence of the linear markings of the peripheral zone. Second stage: A distinctive distribution of small rounded densities, varying in size from a pinhead to a pea, throughout both lungs. The nodules appear first on the right side, around the root of the lung and are perceptible here before they are seen on the left side; when the distribution becomes general there is no appreciable difference between the two sides. Third stage: This is characterized by diffuse fibrosis and may present any or all of three definite and distinctive appearances: (1) The larger nodules of the second stage, where numerous, may coalesce into large, irregular masses, or be found close together with more or less haze between them; (2) a more or less diffuse fibrosis somewhat similar to the fibrotic process representing the late result of an extensive, bilateral, chronic pulmonary tuberculosis. Usually definite nodules are still present, but not always; (3) massive fibrotic areas having the appearance of extensive pulmonary consolidations. In the late period of the disease there is usually one such area on each side, rather symmetrically located subapically, but sometimes unilateral or more extensive on one side than on the other.

The Bone and Joint Changes of Leprosy.—Bone and joint changes of a remarkable and sometimes spectacular type occur with fair frequency in leprosy. According to CHAMBERLAIN, WAYSON and GARLAND (*Radiology*, 1931, 17, 950) it is a surprising fact that clinically advanced cases will often show little or no osseous disturbance, while cases with merely mild clinical signs may show marked changes upon Roentgen examination. Cases of the latter type have predominantly nervous lesions in many instances. Bone absorption—a disappearance of bony tissue without antecedent demineralization—is the most constant finding. This varies from slight metaphyseal narrowing to diffuse diaphyseal absorption or “concentric atrophy.” Complete disappearance of the bone may occur. The absence of bone production is a conspicuous feature. It is probably that the absorptive changes are not specific but are produced directly through nerve involvement. Bone destruction with rarefaction is a less common finding. When present it is believed to be due to specific leprous osteitis, though secondary pyogenic infection may play a part.

Clinical and Experimental Lead Poisoning: Some Roentgenologic and Anatomic Changes in Growing Bones.—CAFFEY (*Radiology*, 1931, 17, 957) reports 3 cases of chronic lead poisoning in children, all of which showed changes in the roentgenograms of the long bones. The roentgenologic changes consist of an increase in density of the growing portions of the skeleton, whereas the slow growing and nongrowing portions of the skeleton appear normal. In 2 children who had recovered, a series of transverse lines was observed in the diaphyses and linear rings of density in the ossification centers of the epiphyseal cartilages and the carpal bones, similar to those which have been reported as pathognomonic of healed scurvy.

Roentgenologic Evidence of Chest Tuberculosis in Tuberculin-positive Ambulatory Children.—The material used in this study by STONE and WOLFF (*Radiology*, 1931, 17, 940) consisted of 93 tuberculin-nega-

tive and 197 tuberculin-positive children who were ambulatory and had no marked symptoms. Forty-two per cent of the tuberculin-positive group had roentgenographic shadows which the writers considered diagnostic. The percentage of such findings was much larger in those cases with the most marked tuberculin reaction. The findings included caseous glands, so enlarged that the resultant tumor projects beyond the vessels, and tuberculous infiltrations in the parenchyma.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

The Neural Symptoms and Signs in Pernicious Anemia.—SMITH-BURN and ZERFAS (*Arch. Neurol. and Psychiat.*, 1931, 25, 1100) report their studies upon 115 cases of pernicious anemia which had been observed for periods varying from 1 to 43 months—the average period of observation being 18½ months. The symptoms and signs referable to the neural system that they observed were: paresthesia, anesthesia, hyperesthesia, impaired sense of vibration, impaired muscle and bone sense (including position), impaired touch, pain and temperature sense, ataxia, altered tendon reflexes, altered cutaneous reflexes, loss of sphincteric control (retention or incontinence), girdle sensations and impaired equilibratory sense, and mental symptoms including depression, irritability, slow thought or speech, hallucinations, illusions, disorientation, ideas of persecution, homicidal tendencies and flight of ideas. Of all the neural symptoms, paresthesia was by far the most common. It was present in 95.6 per cent of the cases. The next in frequency was mental depression, 51.3 per cent; then muscle pains, 42.6 per cent; ataxia, 41.7 per cent; obtunded tendon reflexes, 35.6 per cent; impaired muscle and bone sense, 33.9 per cent; loss of memory, 29.5 per cent; irritability, 27.8 per cent; slow thought or speech, 24.4 per cent; introspection and self pity, 22.6 per cent, exaggerated tendon reflexes, 16.5 per cent; disorientation, 14.7 per cent; joint pains, 13.9 per cent; ideas of persecution, 8.7 per cent; loss of sphincter control, 6.9 per cent; illusions or hallucinations, 6 per cent; psychosis, 6 per cent; homicidal tendencies, 2.6 per cent. The patients were all treated with potent fractions of liver except 3, who were given desiccated hog's stomach. All received sufficient amount of this medication to keep their red blood cell level within the normal range with the exception of a comparatively small group upon whom a determination of the maintenance dosage was done. As a result of their observations the authors conclude that: (a) Improvement may occur in the neural and psychic changes in patients with pernicious anemia under treatment with adequate amounts of liver extract; (b) in some cases arrest of the neural and psychic symptoms, without improvement or retrograde

change, may occur; (c) neural and psychic changes may develop for the first time or may steadily progress while the patient is being treated with daily amounts of liver extract adequate to maintain a normal erythrocyte level; (d) liver extract does not contain a specific anti-neurotoxic substance.

The Status of Probation.—SHELDON GLUECK (*Mental Hygiene*, 1931, 15, 290) states that probation is an evolution of the common-law method of conditionally suspending a sentence. Its origin for all practical purposes began in August, 1841, with the work of John Augustus, who was the first to undertake the supervision of large numbers of offenders, and who performed such tasks as obtaining employment for them, assisting their families, and the like. Probation grew quickly and spread widely because of a natural human tendency to do the latest thing and to seize upon any new device as a panacea. All through the history of penology this tendency is found at work: first, it was the Pennsylvania congregate and silent system of the penitentiary régime that was soon extensively copied; then, it was the Auburn system of work and recreation in common and isolation at night; then, it was the reformatory panacea of introducing into the régime various measures, such as the grade system, schools, military drill, and the like; then, it was probation and parole that spread so rapidly before their principles could be carefully worked out. Massachusetts was the first state in the world to have recognized the importance of this work by providing for public officials to undertake it. Today, every state except Wyoming has a probation law applying to children; 34 states and the District of Columbia have adult probation; only recently probation was extended to the Federal Courts. In 1927, the number of paid and volunteer probation officers throughout the world was estimated as 20,000; recent reports show that there are over 4000 probation officers in the United States alone. Probation in practice varies all the way from merely "letting the offender off" without more than the usual "supervision" by means of having him report periodically at the probation office, to the most advanced application of modern methods of rehabilitation. In too many places probation work is superficially conducted instead of being "intensively cultivated." Probation work should consist essentially not of "letting the offender off easy" or "giving him another chance," but of taking definite steps to help him avoid misconduct in the future. It is an indisputable fact that in a good many courts in the United States, probation officers are appointed who have not the slightest technical equipment for their tasks. However, the practical experience with life that many an untrained probation officer brings to his job is too valuable to be ignored. What is really needed is a combination of scientific training and maturity of outlook on the problems of life. For the attainment of this the author recommends that the probation offices of a metropolitan district, under the guidance of the board of probation or a similar body, arrange for courses in social case work, psychology and criminology, to be taken by probation officers on two or three afternoons and evenings a week. Future candidates for probation work should be required to have had training in these fields in addition to whatever other pertinent experience they may have. Another outstanding factor in probation work is the inadequacy of

investigations. It is quite obvious that in order to be just to the offender the investigation of the case should be intensive. By "intensive" the author means that the offender himself should be examined psychiatrically, psychologically and physically, and a report on his condition from these points of view should be made; full data with regard to his behavior, his school record; and his industrial career should be secured from appropriate sources; the environmental conditions surrounding him and his family should be ascertained; an estimate of the probable etiologic factors in the case should be made and recorded; and on the basis of these findings and of interviews with the dependent, a plan of treatment should be worked out. The plan should be definitely regarded as tentative, and should be modified from time to time in the light of the results. The supervisory work should consist of frequent visits to the family and the focusing of the community's educational, vocational and social resources on the problems presented by the probationer and his family, and not the mere occasional reporting of the probationer at the office to have his name checked off. Record keeping is an important part of the work of probation. Many probation offices in this country cannot tell how many probationers they have at any one time; there are offices in which records of the number of investigations are not kept separately from records of the number of supervisions. There are few offices that publish an annual report. A research unit in every large probation office is necessary—is indispensable in regulating the work and growth and "personality" of this office. The author further points out that criminal law is a stepchild of the law schools—taught today much the same as it was 50 years ago—by the youngest, least experienced teacher; that it is usually taught 2 hours a week instead of 3, and for only one semester instead of two. In the courts the least experienced or weakest judge is usually assigned to criminal cases—or a judge behind in his civil business is allowed to catch up by an assignment to the criminal branch. Criminalistics must be raised to a plane of dignity in the curricula of the law schools. Students interested in criminals should be given more time to study criminal law. And judges should be specialized in criminal work, for this administration of criminal justice is a fulltime, man-sized job. It should not be made a "stop-gap" or "side line."

A General Symptom in Brain Tumor.—KLIMKE (*München. med. Wchschr.*, 1931, 77, 50) presents 4 cases of cerebral tumor in which Kehrer's two signs were demonstrable in unmistakable fashion. The first of these comprises the production of pain on deep pressure over the back of the neck a little to one side of the midline, at the site of emergence of the great occipital nerve. Associated pain reactions consist in flushing of the face, and flexion of the head and neck backward and to the homolateral side. Kehrer's other sign consists of pain on deep pressure over the points of emergence of the three branches of the trigeminal nerve on the face. While this maneuver may cause pain on one side only or perhaps merely in one or two of the branches in cases of tic douloureux and of migraine, in patients with cerebral tumor all six points are painful on pressure. The author believes that these are early and valuable signs of increased intracranial tension analogous to

the demonstration of papilledema. He states that further research is required to determine which of the two signs can be elicited first and whether there is any correlation between priority of appearance and site of the neoplasm.

Pain Pathways in the Sympathetic Nervous System.—MIXTER and WHITE (*Arch. Neurol. and Psychiat.*, 1931 15, 986) present clinical evidence suggesting that sensory impulses may pass over pathways running in or intimately associated with the ganglia of the sympathetic chain and the white rami. They remark that the conception that sensory impulses are carried only by the cranial and spinal nerves has been held and taught for many years—that such a conception is hard to disprove. The conception of the anatomy of the sensory pathways in the sympathetic system to which they adhere is as follows: Pain-bearing nerve fibers probably run in many of the sympathetic nerves that course along the bloodvessels of the head and neck. Whether these fibers are connected with the sympathetic ganglia of the head they do not know, but believe that it is possible. They do not believe that any of these fibers enter the central nervous system above the first white rami above this level, and suggest that they may enter as low as the second and third. Pain pathways from the arm may enter through the sympathetic rami as low as the third and fourth dorsal. They think that pain from the aortic arch and the heart enters the spinal cord from the upper five or six dorsal sympathetic ganglia, and that it may reach the ganglia by two different routes: (1) One route is over the middle and inferior cardiac nerves to the cervical sympathetic trunk. As there are no white rami joining the cervical sympathetic with the cord, the pain fibers must descend at least to the first dorsal segment before they can enter the central nervous system. (2) A second set of gray rami runs from the posterior cardiac and pulmonary flexures directly across the posterior mediastinum to the second, third, fourth and sometimes to the fifth and sixth ganglia. They also believe that from the course of the splanchnic nerves, pain from the upper abdominal viscera enters the cord in the dorsal region, probably from the fifth dorsal to the first lumbar sympathetic ganglia. The technique used was: As a diagnostic measure they injected procain hydrochlorid into the ganglia believed to play a part in the picture. If the result seemed satisfactory, the ganglia were removed, or alcohol was injected into them, or the communicant rami were severed. Cases presented were: Two cases of atypical neuralgias of the face in which a complete removal of the cervicodorsal and second dorsal ganglia was done in 1 case with complete relief, cervicodorsal and the second dorsal ganglia in the second case with only partial relief; 1 case of causalgia of the hand in which the two upper dorsal ganglia were removed with complete relief; 1 case of syphilitic aneurysm of the aortic arch with radiating pain, alcohol was injected into the first and second communicant rami with complete relief; 19 cases of angina pectoris in which the dorsal ganglia were injected with alcohol and 4 in which dorsal ganglionectomy was performed with satisfactory results; 1 case of thoracic and gastric crises of tabes dorsalis in which the seventh to ninth ganglia were removed, the great splanchnic nerve was severed and the fourth

to the seventh rami cut with complete relief of pain. The results which the authors obtained in these cases have caused them to conclude that these patients suffering from the severest types of pain were relieved by interruption of the dorsal sympathetic fibers, and, that there may be definite sensory pathways running in the dorsal sympathetic chain.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Pneumococcus Vaccine Introduced in the Upper Respiratory Tract.—Animal experiments reported by STUPPY, CANNON and FALK (*J. Prev. Med.*, 1930, 5, 97) have shown that the daily insufflation of heat killed suspensions of pneumococci of Types I and II into the nose and throat of rabbits produces active immunity. There was no protection after intraperitoneal injections of living, virulent pneumococci against any bacteria other than those of the type used to immunize the animal. Following vaccination by this method the intratracheal insufflation of living, virulent pneumococci produced a changed type of tissue reaction in the lungs of the animal in which the macrophage was the predominant cell, accompanied by a considerable number of eosinophils, in contrast to the usual polymorphonuclear reaction. This was interpreted as being evidence of a definite type of tissue immunity, which was, however, only relative, since heterologous cultures of living pneumococci produced the same type of local immune reaction but to a lesser degree. Acid killed suspensions of pneumococci were fed orally to humans by Ross (*Proced. Soc. Exper. Biol. and Med.*, 1931, 28, 822) and their serum tested for antibody content by its ability to protect mice injected with fatal doses of pneumococcus culture. In the serum of a number of the subjects there was clear evidence of an increase of antibody content. In some the result was in doubt, while in others no effect could be detected. The absence of demonstrable antibodies in the serum, however, may not mean the lack of an increased resistance to the microorganism since animal experiments seem to indicate that, in some individuals active immunity may be produced without their development.

A Cytopathologic Study of Acute and Chronic Morphinism in the Albino Rat.—Studies on acute and chronic morphinism in the albino rat were undertaken by WEN-CHAO MA (*Chinese J. Physiol.*, 1931, 5, 251). In acute morphinism in animals which had received a single large dose, the injection of the drug is followed by a period of stimulation lasting from 1 to 5 hours. Cytopathologic examination of muscular, nervous and epithelial tissues revealed that the Golgi lipoid, which the

author regards as a special material dissociated from the mitochondria, has become greatly increased in amount, while the mitochondria themselves remain in a normal condition. The initial stimulating effects of the drug are followed by a period of depression (6 to 11 hours after the last injection) in which the Golgi lipid becomes greatly decreased while the mitochondria are slightly increased. Chronic morphinism was produced by daily administration of this drug, over a period of 8 months. In the "craving periods" (2 to 3 days after the last injection) the lipid is greatly decreased while the mitochondria are moderately increased. When the craving is satisfied with an injection of morphin the lipid is found to be moderately increased while the mitochondria maintain their normal appearance. As the animal again passes into the craving period, the lipid gradually decreases. When the animal receives regular administrations of morphin, no deviation from the normal is found. When no more morphin is given, however, the Golgi lipid almost disappears and the rat becomes very inactive. If, however, animals from which morphin had been withheld were fed on lecithin, neither the Golgi lipid nor the animal's activity was reduced.* The author suggests that the result of this study may possibly form a basis for a rational method of treatment in human morphin addiction.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Mechanism of Natural Immunity to Diphtheria. Preliminary Report of Experiments in Puerto Rico.—The extensive studies of specific immunity to diphtheria which have been made in the last 30 years, especially since the development of the Schick test, have shown that antitoxic immunity is related in a very regular way to age. Diphtheria antitoxin sufficient to give a negative Schick test is present, at birth, in the blood of babies born of Schick-negative mothers; but this immunity, which is shown to be passively received from the mother, is gradually lost, so that, before the end of the first year of life, the great majority of infants have become Schick-positive. Thereafter the proportion of Schick-negatives increases steadily with each year of age until, at adolescence, 70 to 90 per cent show this evidence of immunity. The study reported by GARRIDO-MORALES and MANDRY (*Am. J. Hyg.*, 1931, 14, 89) was planned to test, by direct observation, the theory that the change from Schick-positive to Schick negative is mainly due to sub-clinical infection, and at the same time to give more exact information on the prevalence of carrier infections by means of observations repeated

at short intervals. It will perhaps add to the interest of the results that they refer to a tropical country, where clinical diphtheria is relatively rare. The paper includes only the results obtained during the first 3 months of a study which is being continued. The authors found that Schick tests of 642 children attending one of the larger public schools in San Juan, Porto Rico, showed higher proportions of Schick-negatives than usually have been found at corresponding ages in New York, Baltimore and other cities in the northern United States. This accords with previous observations in the Tropics. Bacteriologic examinations made at the time of the first Schick tests (March, 1930) showed 1.4 per cent of the children to be carriers of virulent and 5.8 per cent to be carriers of avirulent diphtheria bacilli. Carrier infections, both with virulent and with avirulent organisms, were somewhat more frequent in Schick-positive than in Schick-negative children. Bacteriologic examinations of 194 originally Schick-positive children, repeated weekly for a period of 3 months discovered a total of 26 (13.4 per cent) carriers of virulent and 42 (21.6 per cent) carriers of avirulent diphtheria bacilli. All those found carrying virulent organisms were previously or later found harboring avirulent bacilli. During the 3 months of observation, negative Schick reactions developed in 85 per cent (22 of 26) of the demonstrated virulent carriers, in 12 per cent of those found carrying only avirulent organisms, and in 9.5 per cent of those showing no positive cultures. Of the four demonstrated carriers of virulent organisms who remained Schick-positive at the end of June, two showed negative, and two positive reactions, when retested the following September. Twenty of the 22 known carriers of virulent bacilli who had developed negative Schick reactions before June 30, were retested 3 to 5 months later. Sixteen of the 20 (80 per cent) were found still Schick-negative, while the remainder showed positive reactions. The completeness and durability of the negative Schick reaction developing after demonstrated infection with organisms classed as virulent showed some relation to the degree of toxicity of the cultures.

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ORIGINAL ARTICLES.

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID
TISSUES.

VII. THE NUCLEOTIDE THERAPY OF AGRANULOCYTIC ANGINA,
MALIGNANT NEUTROPENIA AND ALLIED CONDITIONS.

AN ANALYSIS OF 69 CASES.*

BY HENRY JACKSON, JR., M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, AND ASSOCIATE,
THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL,

FREDERIC PARKER, JR., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, HARVARD MEDICAL SCHOOL;
ASSISTANT PATHOLOGIST, BOSTON CITY HOSPITAL,

AND

F. H. L. TAYLOR, PH.D.,

ASSISTANT, THORNDIKE MEMORIAL LABORATORY,
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, 2d and 4th Medical Services (Harvard),
the Pathological Laboratory, Boston City Hospital, the Department
of Medicine and the Collis P. Huntington Memorial Hospital,
Harvard University.)

In a preliminary paper¹ we reported the results of the treatment of 20 cases of agranulocytic angina and other forms of malignant neutropenia of varied etiology by the intravenous and intramuscular injections of pentose Nucleotide K96.† We use the term agranulo-

* The expenses of this work were defrayed in part by grants from two anonymous donors and from the Smith, Kline and French Laboratories, Philadelphia.

† This material is prepared and distributed by the Smith, Kline and French Laboratories, Philadelphia, under the direction of the Nucleotide Committee of the Harvard Medical School.

cytic angina to cover those cases in which, without known etiology, there is extreme lowering of the white blood cell count and polymorphonuclear neutrophils. The condition is usually acute and there are generally pronounced ulcerative lesions in the mouth or other mucous membranes. We use the term malignant neutropenia in this paper to cover those cases in which extreme leukopenia has followed a definite septic process as, for instance, pneumonia or pansinusitis. The etiology of the two types of neutropenia appears to be different; the prognosis the same.

Since our preliminary publications¹ there have been treated, adequately, 49 additional cases, making a total of 69. Of these 69, 51 (74 per cent) completely recovered. In the most recent analysis of this type of case Taussig and Schnoebelin found that only 25 per cent of 328 collected cases recovered without special therapy;² these authors, after excluding those cases which terminated fatally within 48 hours of the time treatment was instituted, found that 47 per cent recovered when treated by Roentgen ray, 37 per cent when treated with blood transfusion and 27 per cent when given arsphenamin. They also found that only 25 per cent of 178 cases recovered following miscellaneous forms of treatment.

We are greatly indebted to the various physicians under whose care these cases were at the time of their treatment. Without their coöperation, this report would not be possible.

A brief analysis of our own results following the use of Nucleotide K96 is presented.

Patients who died less than 72 hours after treatment was begun, or those in whom treatment was discontinued within this period, have been excluded from this report. A similar selection has been practised by other investigators. Those patients who received only a very brief treatment and then recovered were also excluded because we believed that the treatment was too short to have effected the improvement seen. The preparation was also used in a number of cases of idiopathic aplastic anemia or leukemia. These cases are not included, as the material appears to be of no value in these diseases.

Of the 69 adequately treated cases, 54 were typical agranulocytic angina. Of these 54, 38 (70 per cent) recovered and are to date well. Seven of these cases relapsed after a period of weeks or months but again responded as before to a second treatment with Nucleotide K96. Two cases (Nos. 13b and 39), died in fulminating relapses. In our statistics a recovery is ascribed but once to a case, no matter how many times it may have relapsed and again responded. A case responding favorably once but dying in a subsequent relapse is counted as a death only.

The time and type of response was similar in most cases. The consistency with which hematologic improvement occurred about the fifth day, as recorded in our first paper,¹ has been borne out by

the observations on the additional 49 cases. In 74 per cent of the cases responding, whether agranulocytic angina or sepsis with leukopenia, the white blood cell count began to rise on the fourth, fifth or sixth days following the initiation of treatment, irrespective of the duration of the illness prior to treatment (Chart I), and it continued

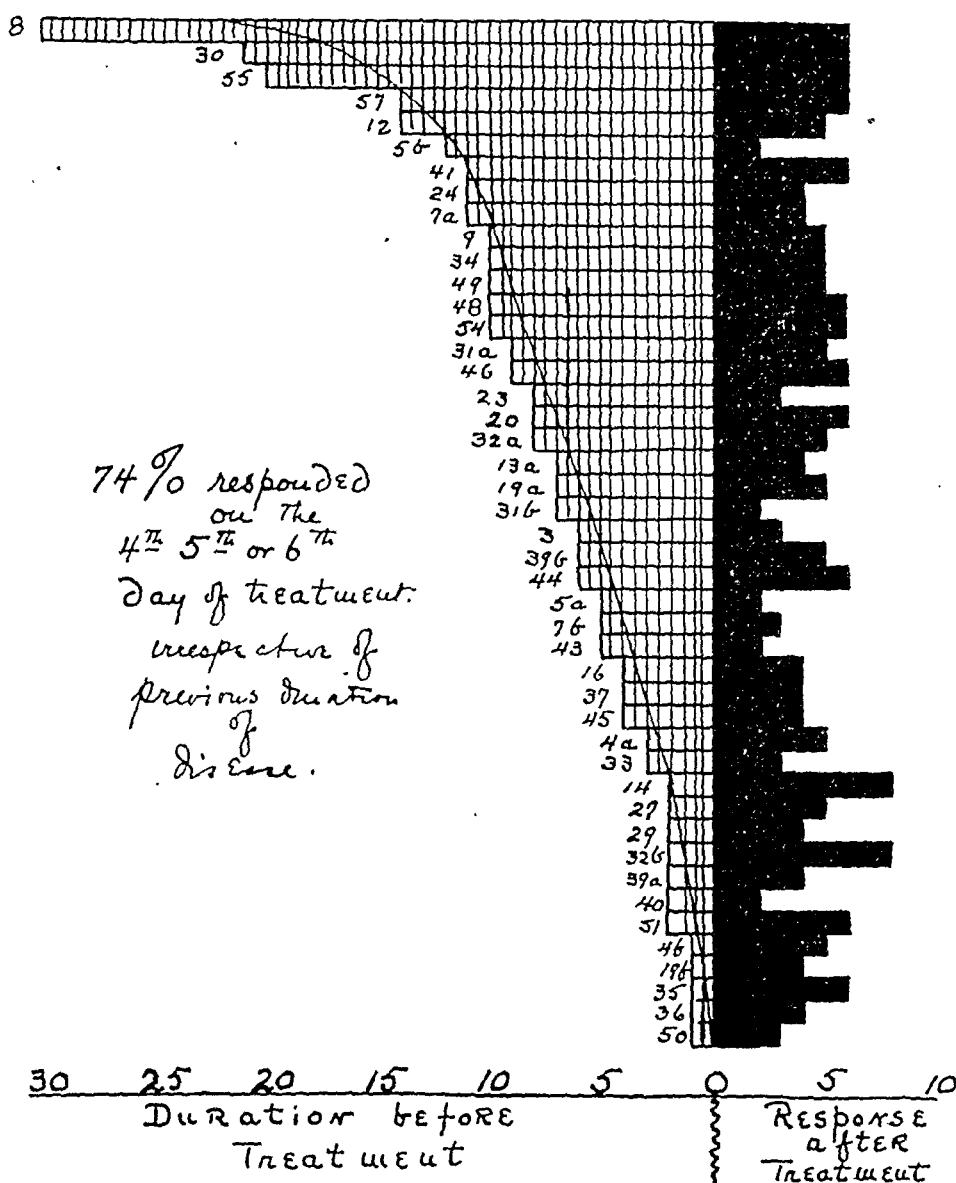


CHART I.—Duration of disease before treatment and time of response after treatment in days.

to rise uninterruptedly from that time on until a high normal figure had been reached, as a rule on or about the tenth day of Nucleotide therapy. If the median white blood cell count for all cases be charted, it is seen that the rise occurs sharply on the fifth day (Chart II). In cases very carefully studied it was usually noted that

a few young polymorphonuclear neutrophils appeared within 48 hours. Unequivocal improvement was usually somewhat later and it is to this pronounced improvement that we refer. The constancy with which improvement began about the fifth day of treatment, irrespective of the duration of the disease, we believe to be an important indication of the effectiveness of the product. In each instance the illness was dated from the beginning of continuous symptoms, although in several cases temporary premonitory symptoms had been present weeks before (No. 41). In virtually all cases the temperature fell to normal a day or so after the first definite rise of white blood cells. Only rarely was there a temporary elevation of temperature once a normal level had been reached.



CHART II.—Median and average polymorphonuclear neutrophil counts of all cases from the beginning of treatment to recovery.

In 1 case of agranulocytic angina (No. 19a), pyelitis with pus in the urine developed suddenly as the white blood cell count approached normal and the same sequence of events was seen in a relapse of the same case (No. 19b). In another case (No. 27) a periappendiceal abscess developed as the white blood cell count rose and the abscess was then successfully drained. In a third case (No. 35) a very large ischiorectal abscess developed with great rapidity after the white blood cell count had reached 6000 per c.mm., and in another (No. 31) suppuration of the cervical lymph nodes took place during early convalescence. Appropriate treatment, often surgical, should be instituted for these complications which are, in a sense, signs of impending recovery. In some instances surgical intervention may be of the greatest importance in removing the source of infection. In 3 of these cases with suppurative complications, there was a sharp temporary drop in the white blood cell count at the time the complication arose, followed by an equally

rapid resumption of the previous upward trend of the white blood cell count. Our interpretation of these findings is that the complicating lesions were present before the obvious local signs were manifest, but that in the absence of polymorphonuclear cells the usual inflammatory response could not take place until the bone marrow had at least partially recovered. That the late infections, in and by themselves, caused the rise in white blood cell count is militated against both by the fact that in 3 instances the white blood cell count was already markedly increased and that in all cases other ulcerative lesions were manifest (without pus formation) from the beginning of the disease and yet they did not cause any increase in white blood cells.

Of the agranulocytic angina cases 87 per cent were females; 2 cases were in the 1st decade of life, 3 in the 2d, 9 in the 3d, 11 in the 4th, 11 in the 5th, 17 in the 6th, 9 in the 7th and 3 in the 8th.

The average duration of the disease before the institution of Nucleotide treatment was 7.2 days. Unquestionably the initiation of therapy earlier in the disease would further decrease the mortality, although certain fatal cases as No. 47 in which treatment was begun the moment the disease was suspected, are so fulminating that no treatment at present available would probably be successful. This patient died on the morning of the 4th day of the disease.

In addition to the 54 cases of idiopathic agranulocytic angina, 13 cases of sepsis followed by extreme leukopenia and neutropenia, were treated. Of these, 11 (84 per cent) recovered promptly and completely. The sepsis was of various sorts: pansinusitis (No. 12), infected arteriosclerotic gangrene (No. 51), infantile pneumonia (Nos. 3 and 4). The mode of recovery and the time of the first rise of the white blood cell count in this type of case were identical with those seen in the idiopathic agranulocytic angina cases.

One case responded sharply and characteristically to the first treatment and then over a period of several months had a series of relapses each of which responded temporarily to Nucleotide therapy. Eventual recovery followed another form of treatment so that the case is not included in this series of 69.

Two cases of very severe benzol poisoning were treated. These have already been discussed in our preliminary paper.¹ Case No. 1 was discharged from the hospital September 1, 1931, with a white blood cell count of 4500 per c.mm. Without any especial treatment the white blood cell count remained constantly at this figure until November 1, 1931. The patient was then readmitted and given, intramuscularly, 10 cc. Nucleotide K96 daily for 2 weeks. At the end of this period of treatment the white blood cell count had risen to 8500 per c.mm. and it has remained at approximately this level for the past 5 months. Case No. 2 is entirely well. In each patient a rise of white blood cell count was seen every time Nucleotide K96 was given as noted in the preliminary report.

Many physicians apparently feel that patients with agranulocytic angina or malignant neutropenia and sepsis who have a white blood cell count above 1000 per c.mm. have a much better chance of recovery than those in whom it is below 1000 per c.mm. Of our 69 cases, 33 (48 per cent) had before treatment a white blood cell count of 1000 per c.mm. or less. Of these 33 patients 66.6 per cent recovered as against 74 per cent recoveries in the entire reported series. Of our cases 10 (15 per cent) had white blood cell counts of 500 per c.mm. or below, yet of these 60 per cent recovered. Again the prognosis is often believed to be increasingly poor in cases which have no polymorphonuclear neutrophils. Of our patients 38 (55 per cent) showed a complete absence of polymorphonuclear neutrophils before treatment, yet 76.3 per cent of these recovered. In only 3 of the entire series of cases was the maximum temperature below 102° F. In 26 cases the highest temperature was 105° F. or over. In 1, No. 57, the temperature reached 106.5° F., yet the patient recovered. Of these cases whose temperature reached 105° F. or over, 65 per cent recovered.

Thus very low white blood cell counts, complete absence of polymorphonuclear neutrophils and very high temperatures do not materially affect, in this series at least, the prognosis.

As the series has become larger it has become increasingly obvious that medication, to be effective, must be intensive and continuous. Of the Nucleotide K96 preparation 10 cc. (equivalent to 0.7 gm. of the solid), should be injected intramuscularly twice a day until the white blood cell count has very definitely risen; 10 cc. should then be given intramuscularly once a day until the white blood cell count has been essentially normal on at least 3 consecutive days. Thereafter the patient should be watched for a possible relapse. In certain resistant cases an increase over the usual dose brought a marked increase of white blood cells, after smaller doses had produced little or no effect (Nos. 30 and 51). In desperately ill cases the contents of one vial should be diluted to 100 cc. with warm sterile saline and injected slowly intravenously each morning for 4 days. On the evening of each of the same days, 10 cc. (undiluted) should be injected intramuscularly. At the end of 4 days the intravenous injections may be discontinued but the bi-daily intramuscular injections should be kept up until the white blood cell count has definitely risen, after which daily single intramuscular injections are to be continued until the white blood cell count has been at a normal figure for at least 3 consecutive days.

To the intramuscular injections there are, as a rule, few if any unfavorable reactions attributable to the material. An occasional patient may have nausea, precordial distress and dyspnea, immediately following an injection. Rarely there may be chills and fever several hours later, but we believe that an improved method of preparing the material has largely eliminated these features. To

the intravenous injections there is usually an immediate reaction of dyspnea and palpitation and in an occasional case there may be chills and fever several hours after the injection. The intravenous injection should, therefore, not be used in the presence of myocardial damage.

No improvement is to be expected during the first few days of treatment. In fact the patient may appear to become worse. This is no indication that eventual recovery will not take place and is no reason for discontinuing treatment. The white blood cell count may even fall during the early days of treatment but this fall can be attributed to progress of the disease occurring before the Nucleotide can sufficiently effect the production of white blood cells.

Relapses occurred in 17 per cent of the agranulocytic angina cases and one must be ready to resume intensive Nucleotide treatment if such do occur. If the white blood cell count rises and then, while still under treatment, starts to fall, an increase of dosage is indicated and favorable results may be expected as in Case No. 51.

We believe that no other specific therapy should be instituted during Nucleotide treatment and that only mild local medication is necessary. The continuous swabbing of the lesions with a variety of antiseptics serves only to disturb the patient. The real problem is that of raising the white blood cell count. Careful nursing care, abundance of fluids and as much nourishment as possible are obvious parts of the treatment. Daily white blood cell counts and careful differential counts should be made. Only thus may the course of the disease be adequately followed. Transfusions of blood in our experience have been more detrimental than beneficial. That they may do good in certain cases is not denied but the evidence in favor of this hypothesis is not striking.

As to etiology, we believe that there are 2 classes of malignant neutropenia. First, there is the primary type in which the leukopenia may precede any symptoms by several days (No. 35). In this case the white blood cell count was for 3 successive days at an approximate level of 500 cells per c.mm. and yet the patient felt perfectly well and was at her work. Routine white blood cell counts were done on this patient because she was known to have had several previous attacks of agranulocytic angina. Only on the evening of the 3d day of leukopenia did the temperature suddenly rise to 104° F. and sore throat develop. The progress of this case strengthens our previous opinion that in true agranulocytic angina of the idiopathic type the blood changes precede and condition the striking anginal symptoms. Second, there is the secondary type in which some obvious infection brings about gradual or rapid fall in the white blood cell count. This latter type is seen following osteomyelitis, pansinusitis, liver abscess, pneumonia or staphylococcus septicemia. The prognosis in the two types appears to be the same; equally grave without appropriate treatment; equally

favorable in this series treated with Nucleotide K96. The etiology of such toxic leukopenias as those induced by benzol or arsenic is obvious.

Summary and Conclusions. An analysis of 69 cases of malignant neutropenia treated with pentose Nucleotide K96 is presented; 74 per cent recovered.

That the preparation was, in fact, effective we believe because:

1. The favorable clinical and hematologic response took place rather sharply about the 5th day of treatment, irrespective of how long the patient had been ill prior to treatment.
2. The subsequent hematologic improvement in practically all cases followed the same orderly pattern.
3. The mortality is the lowest of any published series of like size.
4. Certain laboratory studies, to be reported on at a later date, support the clinical data.

NOTE.—These cases were treated by 40 different physicians in 12 different states. Without their kind coöperation the series could never have been attained. We are particularly indebted to Drs. F. T. Hunter of the Massachusetts General Hospital and W. P. Thompson of the Presbyterian Hospital, New York. The following physicians have contributed to the reported series and we wish to express our appreciation of their coöperation. Boston: J. Baty, M. Blair, F. T. Hunter, R. Lee, F. Newton, W. Dameschek, G. Schwartz; Cleveland: W. Payne; Columbus: C. Doane; Denver: W. C. Black; Evanston, Ill.: F. Bureky; Chicago: H. L. Alt; Hartford: J. W. Hutchison; Lewiston, Maine: J. Gottlieb; Milwaukee: B. J. Birk, W. M. Egan; New Haven: W. W. Bunnell, S. J. Goldberg, A. W. Oughterson; New York: J. Lintz, H. Manley, C. Reich, N. Rosenthal, W. P. Thompson, M. J. Stone; Philadelphia: J. Reisinger; Wilkes-Barre: A. R. Feinberg; Portland, Maine: M. Warren; Providence: F. T. Fulton; Rochester, N. Y.: D. Jewett; San Francisco: L. R. Chandler, E. Falconer; Waterbury, Conn.: J. H. McGrath; Youngstown, Ohio: C. Clarke; Richmond-Highlands, Washington: E. J. Lewis.

REFERENCES.

1. Jackson, H., Jr., Parker, F., Jr., Rinehart, J. F., and Taylor, F. H. L. J. Am. Med. Assn., 1931, 97, 1436.
2. Taussig, A. E., and Schnoebelin, P. C.: J. Am. Med. Assn., 1931, 97, 1757.

THE RESPONSE OF RETICULOCYTES TO POTENT DIETS IN SEVERE EXPERIMENTAL ANEMIA DUE TO HEMORRHAGE.

BY JANET RIOCH,

INTERN, STRONG MEMORIAL HOSPITAL,

AND

F. S. ROBSCHUIT-ROBBINS,

ASSOCIATE IN PATHOLOGY, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE
AND DENTISTRY.

(From the University of Rochester School of Medicine and Dentistry,
Rochester, N. Y.)

THE appearance of reticulated red blood cells in the peripheral circulation has for several years been a matter of considerable clinical interest. Investigation has indicated that definite increase

in reticulocytes may be obtained following liver and iron therapy in posthemorrhagic anemias.^{6,3}

This paper reports the results of a study of the reticulocyte response to potent diets in carefully controlled experimental anemias. The animals used are highly standardized dogs, suffering from a severe anemia existing for a period of years due to blood removal.

Methods. The present experiments were carried out on dogs which are being used for the study of hemoglobin and red cell regeneration. The general experimental procedures to which these animals are subjected have been described before.⁵

The experimental animals were born and raised in our kennels and are kept under practically constant conditions with regard to exercise, ventilation and uniform temperature in the dog rooms. The dogs are rendered anemic by four or more bleedings spaced at 1- or 2-day intervals. The desired anemia level of 40 to 50 per cent hemoglobin is then maintained as near a constant as possible by further hemorrhages graded as to frequency and amounts. Some of the hemoglobin values recorded on the tables may appear as high ones. These high figures, however, represent the levels just prior to further removal of blood in order again to reach the desired anemia level. Blood plasma volume determinations are essential since fluctuations of plasma volume must be taken into consideration in estimating the required bleeding. Hemoglobin pigment in grams is determined in every aspirated bleeding. Hemoglobin is measured in the form of acid hematin colorimetrically against a standard which at 100 per cent is equivalent to 13.8 gm. of hemoglobin per 100 cc. The animals are kept on a standard basal ration consisting of a bread mixture prepared in the laboratory. This basal ration bread is adequate to maintain the anemic dog in health for years and yet permits of but minimal hemoglobin and red cell regeneration over and above the maintenance factor. This bread ration is used in the control periods alternating with or combined with other food factors or drugs to be tested. The animals used in this experiment belong to this carefully standardized anemic colony and their response to various diets is well known. The degree of regeneration is measured by the amount of hemoglobin produced each week over and above the maintenance factor. This maintenance factor indicates the hemoglobin and red cells used up by the general wear and tear of the circulation in the body. We also speak of a "carry over." By this is meant that a dog on a favorable diet will store somewhere in its tissues or organs the ingredients for hemoglobin and red cell construction which later during unfavorable diet periods will be drawn upon for the manufacture of hemoglobin and red cells.

It must be emphasized that the bone marrow is under sustained maximal stimulation because of the long existing anemia and repeated bleedings. The diet is adequate for general maintenance requirements. There were no complicating factors of an infectious or toxic nature. After the control period on the standard bread diet lasting 2 or more weeks, diets known to be very potent for hemoglobin regeneration were fed during a 2-week period which was again followed by the control basal bread ration. In one case, iron was administered intravenously. Daily reticulocyte and erythrocyte counts were made in addition to the usual weekly sampling and blood volume determinations, all blood being obtained by jugular puncture. For reticulocyte counts, the wet method was used. As the blood flowed freely from the needle in the jugular vein, a small drop was rapidly transferred on the tip of a glass rod to a cover-slip. The cover-slip was then gently inverted on a slide on which a film of 0.5 per cent alcoholic solution of brilliant cresyl blue had been dried. The preparation was rimmed with

vaseline and the number of reticulocytes in 1000 red cells were counted under oil immersion. Care was taken to count all of the cells in several different areas of the slides in order to avoid errors due to clumping of reticulocytes. The number of reticulocytes per cubic millimeter of blood can be readily calculated from the total red blood cell count and the reticulocyte per cent.

Dry Method. Permanently stained smears, using the method of Hawes¹ and Cunningham,² were made in one series of experiments. It was found that the cells failed to stain well with the brilliant cresyl blue. A satisfactory explanation of this has not as yet been found. It is possible that the cells did not remain sufficiently long in contact with the dye, before the smear was pulled. Increased speed of coagulation necessitated immediate pulling of smears. Citrated blood was not used. There is a possibility that there is some change in the permeability of the red cells of the anemic dog. They are known to be much less fragile than the normal. Because of the discrepancies in the results obtained by the dry method, they are not included in this paper.

Experimental Data. The blood picture, in general, presented by these animals is that of an extreme, secondary anemia, with anis- and poikilocytosis and erythrocytes of very small diameter. Microcytes and what appear to be cell fragments are also present in large numbers. The reticulocytes vary from large pale cells to cells of very small size. The reticulum is often very dense, as noted by Seyfarth in anemias with rapid regeneration.⁴ Normoblasts appear very rarely.

The blood platelets present an extremely interesting picture. They attain an enormous size, approximating in many cases the diameter of a normal erythrocyte. They appear singly or grouped in clusters. In certain instances these platelets are present in extraordinarily large numbers, particularly in Dog 27-241, Table 3.

The detailed observations are recorded in Tables 1 to 6 and show certain points which are worthy of emphasis. In each dog the total red blood cell curve does not parallel the hemoglobin curve, the rise in red blood cell not being proportional to the amount of hemoglobin.

Dog 25-97. This animal has been raised on a liver diet since weaning and has always responded much more actively with hemoglobin regeneration to any diet than the usual anemic dogs. This experiment demonstrates a high reticulocyte level during the control period when hemoglobin regeneration is low. The pre-control period was preceded by a potent dietary régime with much hemoglobin production. When the animal is put on liver and iron which constitutes one of the most potent hemoglobin-building diets the reticulocyte response is only a questionable one. The hemoglobin production during this two-week test diet period amounts to 63 gm. over and above the maintenance level. The total hemoglobin output due to the liver and iron feeding is figured as approximately 120 gm. in this experiment.

The actual reticulocyte per cent increase is but 20 per cent whereas the reticulocyte concentration (red cells x per cent reticulocytes)

shows a rise of 48 per cent. No acute response of reticulocytes follows the various bleedings. When the dog is again placed on the control diet, one notices a definite drop in reticulocytes which reaches a lower level than that during the previous control period. This occurs in spite of a carry over of hemoglobin production of 56 gm.

TABLE 1.—LIVER AND IRON (DOG 25-97, BULL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level.	R. B. C. vol. hemato- krit.	Plasma vol.
		Thous- per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 450* { Liver 300 Fe. 40 mg. Bread (S) 400	July 11	255	4.9	5.2	1.4	49	21.5	1177
	12	210	4.5	4.7				
	13							
	14	323	6.6	4.9				
	15	...	4.0					
	16	140	3.1	4.5				
	17	143	2.8	5.1				
	18	222	3.9	5.7		69	30.6	1058
	19	260	4.0	6.5	16.5			
	20							
	21	204	3.0	6.8	17.5			
	22	180	3.1	5.8	12.3			
	23	125	3.3	3.8				
	24	243	4.2	5.8	67	30.6	
Bread (S) 450*	25	213	3.8	5.6	71	30.7	1034
	26	297	5.4	5.5	17.0			
	27							
	28	155	3.1	5.0	16.6			
	29	69	1.5	4.6	11.2			
	30	100	2.0	5.0				
	31	143	2.7	5.3	67	28.3	
	Aug. 1	141	3.0	4.7	62	27.3	1075
	2	105	2.3	4.6	16.7			
	3							
	4	103	2.4	4.3	11.4			
	5	70	2.0	3.5				
	6	121	3.2	3.8	52	22.4	
	7	144	3.9	3.7				
	8	138	3.3	4.2	45	19.5	1124
	9	140	3.6	3.9				

* Salmon 75, Klim 25.

Table 2 depicts another experiment of liver and iron feeding. The reticulocyte level during the control bread period is considerably below that presented by other dogs of this experimental series.

Dog 24-45 demonstrates a definite reticulocyte response on the 6th day of the potent diet feeding, increasing to 5.8 per cent or a reticulocyte concentration of from the beginning average of 55,000 to 325,000 on the liver and iron diet. This constitutes about a 500

per cent increase in reticulocyte concentration. This result is in marked contrast to the previous experiment, Table 1. Six days later there is another rise to 4 per cent or 264,000 reticulocytes per c.mm. with a subsequent drop to the control level.

TABLE 2.—LIVER AND IRON (DOG 24-45, BULL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level	R. B. C. vol. hemato- krit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 500*	July 7	4.7	18.8	45	19.5	1228
	14	68	1.4	4.9	47	20.3	1256
	15	43	1.1	3.9				
	16	33	1.0	3.3				
	17	37	1.1	3.4				
	18	31	0.9	3.4				
	19	59	1.5	3.9				
	20							
	21	325	5.8	5.6	66	27.9	1155
	22	211	4.4	4.8	15.1			
{ Liver 300 Fe 40 mg. Bread (S) 300*	23	129	3.0	4.3	15.1			
	24	215	3.9	5.5				
	25	75	1.7	4.4	58	25.5	
	26	79	1.8	4.4				
	27							
	28	264	4.0	6.6	90	38.9	1068
	29	70	1.3	5.4	20.5			
	30							
	31	92	1.7	5.4	18.9			
	Aug. 1	39	0.9	4.3	17.0			
Bread (S) 500*	2	17	0.4	4.2	56	24.3	
	3							
	4	17	0.4	4.2	59	24.9	1180
	5	25	0.6	4.1	13.9			
	6	65	1.5	4.3	11.5			
	7	29	0.9	3.2				
	8	26	0.8	3.3	47	21.7	

* Salmon 75, Klim 30.

Dog 27-241 shows the result of the feeding of liver. The reticulocytes again are high in the control bread period which in this case has not been preceded by a potent-hemoglobin regenerating diet. They average 280,000 per c.mm. and 5.45 per cent in spite of low hemoglobin production. On the liver diet there is a marked response lasting 3 days, rising to 676,000 and 11 per cent. This constitutes a reticulocyte concentration increase of 130 per cent. During the second control period there is a drop in reticulocytes to below the initial level, although there is a carry over of hemoglobin production.

We again observed a high reticulocyte count in the first control period and there is considerable variation from day to day, the average for the period being 163,200 per c.mm. and 4 per cent.

With addition of the secondary anemia liver fraction W-635, potent for hemoglobin regeneration, to the diet there is only a questionable reticulocyte response beginning on the 4th day and continuing throughout the period with considerable daily variation. This response is more significant in relation to the drop in the second control period, than it is with relation to a rise after the first.

TABLE 3.—LIVER (DOG 27-241, COACH, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level.	R. B. C. vol. hemato- krit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Gm.	Per cent.	Per cent.	Cc.
Bread (S) 325*	June 27	4.9	42	19.5	820
	July 2	258	4.7	5.5				
	3	285	5.6	5.1	47	22.2	860
	4	312	5.9	5.3				
	5	296	5.6	5.3				
{ Liver A-924-230 Bread (S) 325*	6	557	8.7	6.4				
	7	550	11.0	5.0				
	8	676	10.9	6.2				
	9	324	5.6	5.8				
	10	383	6.5	5.9				
Bread (S) 325*	11	233	3.5	6.7	70	31.5	787
	12	288	4.0	7.2	18.3			
	13							
	14	240	4.0	6.0	19.3			
	15	212	5.6	3.8				
	16	190	3.8	5.0	61	27.0	
	17	138	3.3	4.2				
	18	131	2.8	4.7	53	23.1	805
	19	211	4.6	4.6	13.6			
	20							
	21	181	4.2	4.3	50	21.6	
	22	202	4.8	4.2				
	23	184	4.1	4.5				
	24	280	5.1	5.5				
	25	165	3.6	4.6	57	23.1	797

* Salmon 100, Klim 30.

Dog 23-1. The reticulocyte level is again seen to be high in the first control period. On the addition of liver, plus a secondary anemia liver fraction plus additional iron to the diet, there is a reticulocyte response which seems definite on the 7th day. The reticulocyte response occurs several days after the active regeneration of hemoglobin had begun. There is again a drop in the reticulocyte level during the second control period. This dog differs from the animals described above in that the drop during the first week of the after control period is less than that during the second week, 3.98 per cent and 2.88 per cent averages, respectively.

TABLE 4.—SECONDARY ANEMIA LIVER FRACTION (DOG 24-2, BULL FEMALE, ADULT)

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level	R. B. C. vol. hemato- krit.	Plasma vol.	
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.	
Bread (S) 325*	July	2	126	2.8	4.5	11.9	51	23.5	945
		3	175	3.8	4.6				
		4	...	3.5					
		5	126	3.6	3.5	46	20.1	
		6	229	5.6	4.1				
		7	118	3.2	3.7				
		8	102	3.0	3.4				
		9	176	4.0	4.4	49	22.4	
		10	253	6.5	3.9				
		{Sec. anemia fraction† Bread (S) 325*		11	...	3.5			
12	110			2.9	3.8				
13									
14	253			6.5	3.9				
15	198			4.6	4.3				
16	196			3.7	5.2	59	24.3	
17	176			4.0	4.4	12.2			
18	172			4.3	4.0	12.0			
19	189			5.4	3.5				
20									
Bread (S) 325*		21	209	5.5	3.8	58	24.2	961
		22	176	4.3	4.1				
		23	271	6.6	4.1	54	23.5	
		24	225	4.9	4.6	17.3			
		25	179	4.7	3.8				
		26	129	3.0	4.3	58	23.6	
		27							
		28	106	2.8	3.8				
		29	125	3.2	3.9				
		30	4.7	64	26.3	
Aug.		31	167	3.8	4.4	14.9			926
		1	117	3.9	3.0	10.9			
		2	133	3.8	3.5				
		3							
		4	80	2.5	3.2	52	22.5	
		5	131	4.1	3.2				
		6	122	3.6	3.4	47	20.2	

* Salmon 75, Klim 25.

† 500 gm. fresh liver equivalent.

Dog 27-230. The reticulocyte level in the first control period for 3 days averages 167,000 per c.mm. and 3.67 per cent, which is similar to Dogs 24-2, Table 4 and 23-1, Table 5.

During the administration of iron intravenously there is a definite reticulocyte response which starts on the first day, reaches its maximum on the 4th day amounting to a reticulocyte concentration increase of 167 per cent, continues throughout the test diet

period and carries over into the second control period. The daily variations are of considerable magnitude.

TABLE 5.—LIVER AND SECONDARY ANEMIA LIVER FRACTION PLUS IRON (DOG 23-1, COACH, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level.	R. B. C. vol. hemato- krit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.
Bread (S) 500* { Liver 300 Sec. an. frac- tion† Plus Fe. 220 mg.‡	July 9	4.7	45	20.1	1042
	10	4.7	45	20.1	1042
	11	160	3.9	4.1	-			
	12	155	3.6	4.3				
	13							
	14	317	6.6	4.8				
	15	...	3.3					
	16	161	2.6	6.2	60	24.3	995
	17	192	3.7	5.2	13.2			
	18	171	3.8	4.5	12.3			
	19	352	8.0	4.4				
	20							
	21	428	6.8	6.3	74	33.0	
	22	221	4.8	4.6				
	23	336	7.0	4.8	71	30.2	992
	24	205	3.4	5.9	13.9			
	25	160	3.2	5.0	14.7			
	26	181	4.1	4.4	10.7			
	27							
	28	236	5.9	4.0	56	23.2	
Bread (S) 500* { Liver 300 Sec. an. frac- tion† Plus Fe. 220 mg.‡	29	108	2.7	4.0				
	30	52	22.2	1050
	31	168	3.9	4.3	9.9			
	Aug. 1	119	3.4	3.5				
	2	154	3.5	4.4	53	21.7	
	3							
	4	108	2.7	4.0				
	5	53	1.4	3.8				
	6	152	4.0	3.8	45	19.2	1095
	7	81	2.3	3.5				

* Salmon 75, Klim 25.

† Bread (S) 350.

‡ 300 gm. fresh liver equivalent.

Following a gradual drop we again observe a rise to 420,000. Another rise occurs on the 3d day of the control period. Unfortunately the reticulocyte counts had to be discontinued before the lower bread control level was reached.

Discussion. Diets potent for hemoglobin regeneration produce but a slight or only moderate reticulocyte response under the experimental conditions reported. Most of these animals show a high

reticulocyte level during the control bread period preceding the test diet régime. One also observes marked individual variations in the reticulocyte response elicited. For example Dog 25-97, Table 1, with a high initial level of reticulocytes was fed an optimum diet for hemoglobin regeneration with the usual result of a very

TABLE 6.—IRON, INTRAVENOUS (DOG 27-239, BULL MONGREL, FEMALE, ADULT).

Diet, Grams per day.	Date.	Reticulocytes.		R. B. C.	Hb. re- moved by bleed- ing.	Hb. level.	R. B. C. vol. hemo- krit.	Plasma vol.
		Thous. per c.mm.	Per cent.	Millions per c.mm.	Grams.	Per cent.	Per cent.	Cc.
Bread (S) 400* (Fe, i.v. 20 mg.† Bread (S) 400*	July 28	4.2	39	18.1	800
	29	116	3.3	3.5				
	30	170	3.7	4.6				
	31	204	4.0	5.1				
	Aug. 1	249	5.3	4.7				
	2	258	6.3	4.1				
	3	490	8.3	5.9				
	4	486	9.0	5.4	46	22.1	737
	5	276	5.3	5.2				
	6	209	4.1	5.1				
Bread (S) 400*	7	350	6.6	5.3				
	8	211	3.9	5.4				
	9	255	4.4	5.8				
	10							
	11	234	4.1	5.7	68	31.5	725
	12	420	5.6	7.5	14.3			
	13	346	6.3	5.5	14.1			
	14	285	6.2	4.6				
	15	320	6.8	4.7	57	26.8	
	16	355	7.1	5.0				
	17	460	9.2	5.0				
	18	5.6	66	30.9	747
	19	16.3			
	20	12.3			
	21							
	22	56	24.8	
	23							
	24							
	25	5.1	57	25.3	723
	26	13.6			

* Salmon 75, Klim 25.

† Iron administered as colloidal—Loeser.

high hemoglobin output. As has been mentioned previously this animal has been raised on a diet very rich in liver since weaning and reacts always with much greater hemoglobin manufacture than the other anemic animals of the series. Further stimulation by the liver and iron diet elicits only a very questionable response in reticulocyte output.

Dog 24-45, Table 2, on the other hand, with a much lower reticulocyte level during the control period shows a much more definite reaction to the liver and iron diet as concerns reticulocytes.

If one considers the reticulocyte concentration rather than the percentage rise this increase amounts to 500 per cent in Table 2 as compared to but 48 per cent in Table 1 on the same diet. If one uses this figure for comparison the reticulocyte increases appear to better advantage.

These experiments of course are only a few in number as we were mainly interested in ascertaining whether diets very potent in hemoglobin building properties would also demonstrate a marked increase in the reticulocytes. We observe that in the cases cited feeding the secondary anemia extract gives negative results, adding liver to this diet gives a value just slightly above that of the liver alone. Liver plus iron gave better results than either liver or iron alone. One must remember however that a large series of such experiments may give different results.

One may argue that the red blood cells are at a much higher beginning level than reported in human cases of secondary anemia and that therefore the response would be but a slight one. In considering the bone marrow response of these dogs, however, it must be emphasized that their normal hemoglobin level is approximately 130 to 160 per cent with a red cell count of 8 to 10 millions and that a red cell count of 5 millions in these animals is comparable to one of 3 million in a human being. As the majority of these dogs show red cell figures of 5 million or below at the beginning of the test diet period the anemia level is more severe than one would realize when considering the figure indicated on the tables. These dogs have been kept at an anemia level of one-third of normal for several years. The bone marrow therefore has been under maximal stimulus due to the anemia *per se*, for a long period of time. This is evidenced by the high level of reticulocytes. The added stimulus of a diet, potent in hemoglobin regeneration, does not therefore bring a marked response since stimulus is already nearly maximal. Red cell production might be considered as approaching a normal mechanism in these animals, since there is no toxic factor at work, nor is there any nutritional deficiency. The frequent bleeding masks the level to which the total red blood cell count would rise.

That there is at least some disturbance in the maturation of the erythrocytes, is evidenced, however, by the high control level of reticulocytes. The normal level for dogs is given by Seyfarth⁴ as 0.2 to 0.5 per cent. Under the stress of the demand for erythrocytes, the bone marrow turns out some immature cells with the great mass of mature cells. There does not appear to be a correlation between reticulocyte formation and hemoglobin output. The reticulocyte level might be as high with a 10 gm. hemoglobin output as with one amounting to 100 gm. of hemoglobin.

Summary. The response of the reticulocytes on feeding potent diets for hemoglobin regeneration to dogs suffering from a long continued severe anemia produced by blood removal has been compared with the reaction due to the feeding of the basal bread ration. The reticulocyte level shows considerable individual variation. The results obtained demonstrate only a slight or moderate reticulocyte response to diets very potent for hemoglobin regeneration. There seem to be two factors in the potent diets fed. The most important one is the factor influencing hemoglobin regeneration. The second assists in stroma formation.

NOTE.—We gratefully acknowledge the coöperation of Dr. Ethel Simpson MacDonald in preparing the smears for the dry method.

BIBLIOGRAPHY.

1. Hawes, J. B.: A Study of Reticulated Red Blood Corpuscles by Means of Vital Staining: Its Relation to Polychromatophilia and Stippling, *Boston Med. and Surg. J.*, 1909, **161**, 493.
2. Cunningham, T. D.: A Method for the Permanent Staining of Reticulated Cells, *Arch. Int. Med.*, 1920, **26**, 405.
3. Minot, G. R., Murphy, W. P., and Stetson, R. B.: The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *AM. J. MED. SCI.*, 1923, **175**, 581.
4. Seyfarth, Carl.: Experimentelle und klinische Untersuchungen über die vitalfärbbaren Erythrozyten, *Fol. Hæmatol.*, 1927, **34**, 7.
5. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: Standard Basal Ration Bread and Experimental Methods, *Am. J. Physiol.*, 1925, **72**, 395.
6. Yang, C. S., and Keefer, C. S.: The Response of the Reticulocytes in Secondary Anemia Following Various Forms of Treatment, *Arch. Int. Med.*, 1930, **45**, 456.

THE TREATMENT OF SECONDARY ANEMIA WITH "SECONDARY ANEMIA LIVER EXTRACT" AND IRON.*

BY GARNETT CHENEY, M.D.,

INSTRUCTOR IN MEDICINE, AT THE STANFORD UNIVERSITY MEDICAL SCHOOL,

AND

FREDERICK NIEMAND, M.D.,

INSTRUCTOR IN MEDICINE, AT THE STANFORD UNIVERSITY MEDICAL SCHOOL,
SAN FRANCISCO, CALIF.

(From the Stanford Medical Service of the San Francisco County Hospitals.)

DURING the last few years various types of anemias have been investigated extensively, bringing to light new factors in regards their etiology, their classification and their treatment. Whipple may be considered the modern pioneer in this field, and his studies on artificially induced anemias in dogs forms the background for

* We are indebted to Eli Lilly and Company for supplying us with their extract. "Secondary Anemia Liver Extract No. 55 With Iron," which has made this work possible.

most of the recent progress, together with Minot's independent application of a high liver diet in the treatment of Addison-Biermer anemia. Whole liver, kidney, stomach, bone marrow, spleen, extracts of these organs, large doses of iron, and copper have risen rapidly to therapeutic prominence, and one is now confronted with the difficult question of when to use one of these, when to use a combination of them, or whether to use any of them in the treatment of a given case. This confusion in therapy is due to the lack of a satisfactory classification of the anemias, to a lack of standardization as regards a uniformity of dosage, and above all to a wealth of reports on a few interesting cases treated in various ways, but almost no reports on large series of cases treated uniformly and carefully controlled. Under such circumstances it is very difficult to evaluate the various therapeutic agents, consequently only liver and iron, which seem to give the most promise, will be discussed.

A brief review of the work of Whipple and his associates¹ in studying anemias in dogs is essential to an understanding of the basis of liver and iron treatment. He and his co-workers produced a severe anemia in dogs by repeatedly bleeding, which was so regulated as to maintain this anemia at a practically constant level. The intake of iron and the diet could be accurately controlled and also the daily output of iron. Many forms of treatment for these induced posthemorrhagic anemias were tried out.

The findings relative to the use of iron are extremely important and present to a certain degree the key to the success of modern iron therapy. They showed that organic preparations had no value over inorganic ones, and that all inorganic salts were about equally efficacious. Of particular importance is the dosage. Although the animals would eliminate all excess iron over a certain dose, real improvement was often only obtained after giving three or four times this dosage. As it has been long thought that the optimum dosage in man would only be as much as he could utilize, more than this was considered unnecessary. However, Whipple has shown in dogs, at least, that three or four times this dosage is often necessary and then may produce excellent results. The reason for this is not yet understood, but it has been suggested that it is similar to the salt action necessary in certain chemical reactions. There seemed to be no advantage in giving iron subcutaneously or intravenously and the oral method was the one usually chosen. Apparently the problem is one of availability of iron and that if a large amount is present, sufficient will be utilized in the formation of hemoglobin.

These same workers also fed liver to their anemic dogs. They found that whole liver often produced a marked improvement and that an extract of whole liver produced some improvement. Extract of a certain fraction of liver was more effective in treating this hemorrhagic type of anemia than the extract of the whole liver.

itself. Finally they found that a combination of liver extract from a fraction of whole liver, which they have designated as a secondary anemia extract, and a large dosage of iron, produced a more brilliant result than all other methods of therapy, except the combination of whole liver and a large dosage of iron. These findings have stimulated extensive clinical investigations along similar lines.

The many clinical reports, however, are not all in accord. A few may be mentioned briefly. Murphy² found that liver extract (from whole liver) is of no value in the treatment of secondary anemias. Wahlberg,³ contributing a study of 19 cases, found that in certain instances liver and liver extract alone seemed effective, and in others they were not effective unless iron was added. Iron alone was most effective in certain instances. Witts⁴ has found this true in a group of cases he has designated as achlorhydric, hypochromic anemias. Keefer⁵ has reported successful therapy with whole liver extract and iron in secondary anemias. A secondary anemia liver extract has not yet been tried on patients, despite the excellent example of its merit which has been proven in animals.

The object of the present study was to observe the response of various forms of human anemia to a standard secondary anemia liver extract to which iron has been added. We wished to determine the extent of the response, when present; to differentiate the types of anemia which responded, and those which did not; and, if possible to discover any criteria which might indicate if improvement could be expected.

Methods. The cases studied included all cases of marked anemia, regardless of type, which were on the Stanford Medical Service of the San Francisco County Hospitals and those cases in private practice in which the treatment could be satisfactorily controlled. The total series consisted of 50 cases which were observed in a period of 8 months. In each instance, the patient was seen and studied clinically by one or both of us.

In all but 3 cases, two trained technicians made the blood examinations and the same technician always made all the examinations on the same individual. Hemoglobin estimations and red blood cell counts were done from one to three times a week throughout the period of study, the frequency of examination depending on the severity of the anemia and the availability of the patient. The hemoglobin examinations were made with the Sahli hemoglobinometer by choice, but at times the Tallqvist method was utilized. In 33 cases reticulocyte counts were made. In a few instances patients were not available for a sufficient number of counts to be of any value. If the red blood cell count was over 3 million, reticulocyte studies were not usually done. Counts were made two or three times a week for the first 2 weeks and frequently throughout the further course of treatment. A count was always made before the treatment was started. The intravital staining method of Wyckoff⁶ was employed and proved satisfactory. As a rule only 200 cells were counted, as variations in reticulocyte per cent, which are less than one-half of 1 per cent are not considered significant. Where no reticulocytes were encountered after observing 200 cells, the count was recorded as less than one-half of 1 per cent, which corresponds to a normal figure. As Price-Jones⁷ and others have empha-

sized the important relationship between red blood cell sizes and successful liver therapy in Addison-Biermer anemia, the average erythrocyte diameters were estimated two or three times a week for 3 weeks, and weekly thereafter. The estimations were made by means of Eve's Halometer as previously described by one of us.⁸ White blood cell counts were carried out in several cases, but have not been included in this report.

The length of time patients should be treated was chosen as 3 weeks, because it was felt that any type of successful therapy would almost surely be demonstrated during this period. It was also felt that this was a sufficient time in which to demonstrate increases in reticulocytes and changes in cell size if such occurred. It is, of course, possible that a case of severe anemia might improve only after 3 weeks' treatment, but there is no good precedent that this is likely. The choice of dosage was a difficult problem, but it was decided to give 12 gm. daily, either in one dose or divided into 3 equal parts. This choice was based on the fact that this was the average dose recommended by the manufacturers of the extract, but it seemed quite likely that larger doses would prove to be efficacious in some cases. Two cases received only 8 gm. daily, while 1 case received 16 gm. daily for a part of the treatment. Two cases received 24 gm. daily. Certain patients were able to take the extract in water without difficulty but others could not. Consequently, the extract was frequently given in whatever vehicle it was best tolerated. Orange juice, grapefruit juice and hot peppermint water often proved satisfactory. No untoward effects on the stomach were noted.

The 50 cases studied have been divided into three groups on the following basis.

The first group is composed of 23 cases in which we felt that a definite disease was responsible for the production of the anemia. Table 1 shows a wide variety of disorders, which are generally accepted as causing secondary anemia. The second group is composed of 14 cases, all of which were secondary to hemorrhages. Most of these patients suffered from chronic hemorrhages, but, in 4 the history suggested that the bleeding was acute (Table 2). Group III (Table 3), includes all cases in which no satisfactory reason for the anemia could be definitely determined. These 13 cases include several examples of what may be called "dietary anemia" and "toxic anemia," but such an etiology could only be suspected and could not actually be proved. Actually every effort was made to determine the clinical diagnosis on all of these 50 cases and it was surprising to find in how many instances it was impossible to come to any agreement as to the exact causative factor.

The tables show the clinical diagnosis, the degree of anemia before their treatment, and the exact length of treatment. For the three groups they also show in the majority of cases the degree of improvement at the end of a 3 weeks period as a basis of comparison. The date and degree of maximum reticulocyte response and the red blood cell size before and after treatment are also recorded. In the last column in each table is noted whether or not the patient improved and this is based upon the changes in the red blood cell count at the end of a 3 weeks period. These results have been arbitrarily divided into three classes and designated as marked improvement, moderate improvement, and no improvement at all.

TABLE 1.—THE RESULTS OF LIVER AND IRON THERAPY IN 23 CASES OF ANEMIA SECONDARY TO SOME SYSTEMIC DISEASE.
(DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.			End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions per c.mm.	Size, micra.	Hgb., %	R.B.C.	Length of treatment, days.	Hgb., %	R.B.C., millions per c.mm.	Size, micra.		
25	Biliary fistula	55	3.9	7.7	..	680,000	15	60	3.1	7.6	None.
42	Lung abscess; sepsis	60	3.9	7.5	6	None	21	66	4.5	7.5	Moderate.
49	Cancer of esophagus	50	3.8	7.7	None	None	19	54	3.8	7.6	None.
3	Colon cancer; empyema	45	3.5	7.6	15	420,000	27	54	3.4	7.5	4th day—7%	None.
20	Cirrhosis of liver	68	3.5	7.7	None	None	21	58	2.6	7.7	None.
19	Pyelitis	50	3.4	..	No record	None	39	65	4.0	Moderate.
36	Pulmonary tuberculosis and pneumokoniosis	60	3.2	7.6	5	None	18	55	3.2	7.6	<0.5%	None.
46	Colon cancer with hemorrhages during treatment	50	3.1	7.7	12	50	3.1	8.0	7th day—1%	None.
35	Cirrhosis and primary cancer of liver	62	3.1	8.0	None	670,000	24	62	3.7	7.7	<0.5%	Moderate.
32	Osteomyelitis	55	3.0	7.5	3	730,000	36	58	3.6	7.6	<0.5%	Moderate.
38	Pulmonary tuberculosis	63	2.8	7.7	4	570,000	20	67	3.4	7.3	14th day—1%	Moderate.
16	Sarcoma of humerus	52	2.6	7.6	None	None	25	50	2.0	7.3	<0.5%	None.
29	Pyelitis; sepsis	45	2.6	7.5	17	40	2.3	8.0	14th day—6%	None.
39	Cancer of ovary	55	2.6	7.6	5	220,000	21	60	2.8	7.5	11th day—1%	None.
37	Pulmonary tuberculosis	52	2.6	7.7	None	None	18	50	2.6	7.6	14th day—0.5%	None.
50	Cancer of stomach*	46	2.6	7.6	8	500,000	21	54	3.1	7.6	<0.5%	Moderate.
45	Pellagra, pulmonary tuberculosis; empyema	50	2.4	8.0	None	None	21	50	2.0	7.6	<0.5%	None.
44	Cancer of stomach	45	2.4	7.8	3	None	21	48	2.4	7.8	<0.5%	None.
28	Sepsis	55	2.3	7.6	1	550,000	36	58	3.5	7.5	6th day—2%	Moderate.
1	Chronic nephritis	30	2.2	7.3	2	200,000	28	32	2.3	7.3	7th day—5%	None.
48	Cancer of kidney	35	2.2	7.6	5	300,000	30	40	2.4	7.5	11th day—1.5%	None.
12	Lymphosarcoma, stomach	20	2.2	7.5	None	None	19	18	2.0	7.5	9th day—1%	None.
15	Hodgkin's disease	45	1.6	7.8	None	None	24	35	1.5	7.6	18th day—16%	None.

* Patient received 24 gm. daily.

TABLE 2.—THE RESULTS OF LIVER AND IRON THERAPY IN 14 CASES OF ANEMIA SECONDARY TO HEMORRHAGE. (DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.		Length of treatment, days.	End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.	Hgb., %	R.B.C.		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.		
24	Menorrhagia	70	3.9	7.5	3	420,000	21	73	4.3	7.5	Moderate.
41	Abortion	68	3.9	7.5	2	450,000	25	70	4.3	7.5	Moderate.
26	Menorrhagia	68	3.6	7.5	2	320,000	21	70	4.0	7.5	Moderate.
47	Hemophilia	58	3.1	7.2	6	660,000	60	73	4.0	7.3	Moderate.
17	Duodenal ulcer	48	2.6	7.6	11	33	2.0	7.8	10th day—2%	None; cont. bleeding.
18	Hemorrhagic colitis	35	2.4	8.5	5	490,000	59	70	3.8	..	13th day—8%	Moderate.
11	Hemorrhoids	26	2.1	8.0	29	1,000,000	50	70	4.2	7.6	18th day—6%	Marked.
43	Visceral purpura	35	2.1	8.0	16	62	3.4	7.6	Marked.
5	Duodenal ulcer*	35	2.1	7.9	15	1,120,000	57	66	4.5	7.5	17th day—8%	Marked.
30	Gastric hemorrhage; probable cirrhosis	40	2.0	8.3	10	830,000	31	52	3.1	7.8	4th day—6%	Moderate.
34	Acute hemorrhages from fibroid	24	1.9	8.2	33	2,220,000	21	57	4.2	7.6	9th day—8%	Marked.
4	Chronic epistaxis†	20	1.5	8.4	17	1,660,000	60	65	4.4	8.0	Marked.
8	Duodenal ulcer†	30	1.5	8.2	20	1,670,000	21	50	3.2	8.0	Marked.
27	Gastric hemorrhage; ammonia poisoning	30	1.2	8.1	7	30	1.8	7.9	3d day—6%	? Marked.

* Patient received only 8 gm. daily.

† Patient received only 8 gm. daily.

‡ Patient received 16 gm. for the first 10 days of treatment.

TABLE 3.—THE RESULTS OF LIVER AND IRON THERAPY IN 13 CASES OF ANEMIA OF UNKNOWN CAUSE. (DOSE—12 GM. DAILY.)

Case No.	Diagnosis.	Before treatment.			Gain in 3 weeks.		Length of treatment, days.	End of treatment.			Day and degree of highest reticulocyte count.	Improvement.
		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.	Hgb., %	R.B.C.		Hgb., %	R.B.C., millions, per c.mm.	Size, micra.		
6	Anemia, ? cause	65	4.2	7.3	8	741,000	23	73	5.0	7.3	Moderate.
40	Leg amputation; anemia, ? cause	60	3.8	7.8	7	430,000	20	67	4.3	7.5	14th day—1.9%	Moderate.
7	Morphin addict; undernutrition ?	50	3.5	7.6	None	None	25	48	3.8	7.5	25th day—3%	None.
33	Anemia, ? cause	75	3.4	7.4	None	460,000	36	81	4.7	7.4	Moderate.
9	Neuritis; anemia, ? cause	68	3.4	7.6	None	400,000	32	72	4.3	7.5	Moderate.
13	Tubes and As. therapy	34	3.3	7.7	8	270,000	21	42	3.5	7.5	None.
21	Spastic paralysis; anemia, ? cause	65	3.2	7.9	10	78	4.0	? Marked.
31	Gonorrhea; ? dietary anemia	53	3.0	7.6	14	450,000	19	65	3.5	7.2	3d day—3%	Moderate.
22	Bulbar paralysis; ? dietary anemia	42	2.6	7.6	6	680,000	43	65	3.8	7.3	8th day—3%	Moderate.
23	Gastritis; ? dietary anemia	50	2.3	7.6	15	1,190,000	21	65	3.5	7.5	7th day—6%	Marked.
23	Anemia, ? cause*	45	2.1	8.0	13	840,000	24	60	3.0	7.7	<0.5%	Moderate.
10	Anemia, ? cause	18	1.6	8.5	14	490,000	44	42	2.8	8.5	9th day—3%	Moderate.
14	Lues and As. therapy	30	1.5	8.2	26	790,000	43	65	3.2	..	21st day—8%	Moderate.

* Patient received 24 gm. daily.

As in cases of Addison-Biermer anemia which respond well to liver therapy there is usually a gain of about 1 million or more red blood cells in the first 3 weeks of treatment, all the cases of secondary anemia which made this same striking increase are classed as marked improvement. Those cases which gained about 500,000 red blood cells and some hemoglobin are classed as moderate improvement, although it is quite certain that such gains might conceivably occur without any effect from the therapy. This is particularly true when the anemia follows acute hemorrhages. Nevertheless, when the red blood cell increase occurred corresponding to the liver extract therapy, it was felt justifiable to classify the response as attributable to the mode of treatment. Those cases which made no gain, or even lost, made up the group in which no improvement occurred. Under such a classification borderline cases were bound to occur, and in such instances these cases were included in the less favorable group. The changes in the red blood cell count were chosen as a more accurate indication of response than hemoglobin changes on the basis of similar work in Addison-Biermer anemia. In grouping the cases of anemia for comparison, account has not only been taken of the cause of the anemia, but also of the severity. Those cases in which the anemia was the mildest are listed first in the tables, and the more severe cases are listed in the order of their severity. It must be borne in mind that cases of moderate anemia cannot be expected to improve as strikingly as cases of severe anemia and this must be taken into consideration in comparing the cases in the three tables.

In reviewing the results of therapy in the group of cases included in Table 1 it is evident that anemia secondary to some general systemic condition does not respond well to treatment. Out of 23 cases, 16 showed no improvement whatsoever, and of the 7 cases which did improve, none showed marked improvement. In 10 instances various types of neoplasm were the obvious cause of the anemia, and all of these proved to be therapeutic failures, except Case 50 with a malignant ulcer of the stomach. As this patient gave a history of previous unsuccessful treatment on an average dose of secondary anemia liver extract and iron, we used double the dose, or 24 gm. daily, with remarkable clinical improvement, including a gain in weight and strength. This experience suggests that larger doses might have been more successful in the other 9 cases. When the anemia was caused by chronic infection, the outlook was somewhat better. There were 9 such cases, 4 of which were due to tuberculosis, uncomplicated by hemorrhage. In the nontuberculous group 4 out of 5 cases showed moderate improvement, while only 1 case of tuberculosis improved. Of 2 cases of cirrhosis of the liver the blood count improved in 1, in the other it did not. The patient in which improvement occurred, Case 35, subsequently came to autopsy and showed a small primary cancer of the liver. As he

presented all the usual clinical and autopsy findings of cirrhosis, and as the neoplasm was small, he was not included in the group in which malignant disease was held responsible for the anemia. A case of long-standing biliary fistula, and a case of chronic nephritis in which pronounced anemia was the chief feature for several months failed to improve. On the whole the treatment carried out in this group of anemias was unsatisfactory, except that improvement occurred in the patients with infections where the cause of the anemia might ultimately be overcome.

The results of the treatment recorded in Table 2 are in sharp contrast to those just reviewed. Here the anemia was the result of blood loss, and in all but one of the 14 cases improvement occurred, and in one-half the cases the red blood cell count increased so rapidly that the increase could be compared to that occurring in Addison-Biermer anemia after whole liver therapy. Case 17 which did not improve, continued to bleed extensively and has only been included in the series to emphasize that persistent profuse blood loss will negate the beneficial effects of the treatment. Actually the degree of improvement is even better than indicated in the table, for 3 of the 6 cases designated as moderate, had an initial red cell count of over 3,500,000 when a gain sufficient to be designated as marked could hardly be expected. In 2 further cases, 18 and 47, slight bleeding occurred during the treatment, so that they may not have received the maximum benefit from the liver extract and iron. Six of this group of cases, Nos. 4, 8, 18, 24, 26 and 34 had received iron therapy alone previous to coming under our observation, and without any material improvement being noted. In most instances the dosage was probably less than that given by us, although no accurate data is available. In summarizing this group it seems justifiable to state that the majority of these 14 cases of anemia secondary to hemorrhage were definitely benefited by the secondary anemia liver extract with iron.

It is difficult to interpret the findings in the miscellaneous group of cases recorded in Table 3. A comprehensive report would necessitate a detailed description of each individual case, which is beyond the scope of this paper, and would not disclose the exact cause of the anemia. Of the 13 cases included, 2 showed no definite changes in the blood count for the better, 9 showed moderate improvement during therapy, and 2 cases showed a really marked improvement. It seems probable that some of these cases might have improved moderately on no other treatment than bed rest and the hospital diet, but in other cases, such as 6, 10, 13, 14, 22, 23 and 31 it seemed probable that there was a causal relationship between treatment and improvement. The first of these 7 cases had received iron alone for 4 weeks without benefit. The dose was 12 grains daily. Cases 10 and 23 resembled Addison-Biermer anemia, and each received a course of treatment with Lilly's Liver Extract No. 343.

The blood counts did not improve until Lilly's Liver Extract No. 55 was given subsequently. The other 4 cases were in the hospital under observation from 2 to 4 weeks without improvement in the blood picture until they received specific anti-anemia treatment. Judging from the results obtained in this group of 13 cases it may be concluded that liver extract and iron may be of value in those anemias for which no cause can be found, and that they should be given a trial, if iron alone is unsuccessful.

It is very difficult to evaluate the efficacy of the treatment carried out in the whole series of 50 cases. It can be positively stated that 31 cases (62 per cent) improved coincident with the therapy, but it cannot be positively stated that in each instance the improvement was due to the therapy. Consequently the comparative figures for the three groups of cases shown in Table 4 must be taken guardedly. They may be summarized as follows: (1) posthemorrhagic anemias showed too great a uniformity of improvement to be disregarded: they were benefited; (2) anemias due to systemic disorders such as cancer, nephritis, chronic infections, etc., were not benefited as a group; (3) anemias of unknown etiology were not markedly benefited as a group, although in a few instances the liver and iron treatment seemed of value. Nevertheless, no results were obtained which might not have been obtained from iron alone.⁹

TABLE 4.—COMPARATIVE RESULTS OF LIVER AND IRON THERAPY IN 50 CASES OF SECONDARY ANEMIA.

Degree of improvement.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemorrhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Marked	0 = 0%	7 = 50.0%	2 = 15.4%	9 = 18%
Moderate	7 = 30.5%	6 = 43.6%	9 = 69.2%	22 = 44%
None	16 = 69.5%	1 = 6.4%	2 = 15.4%	19 = 38%

Reticulocyte counts in 33 cases (Table 5) showed results somewhat at variance with the generally accepted idea that a reticulocytosis is indicative of an improvement in the blood count in secondary anemias.¹⁰ Of 24 cases showing an increase in the number of reticulocytes above the normal, 9 (more than a third), failed to show any increase in the red cell count or the hemoglobin per cent. The highest reticulocyte count encountered, 16 per cent in a case of Hodgkin's disease, was one of these 9 cases. We have seen reticulocyte counts up to 14 per cent in cases of untreated secondary anemia which did not improve. Such findings suggest that the reticulocyte, as an immature form of red cell, is indicative of bone marrow activity, but not necessarily successful activity as far as the anemia is concerned. Its appearance in numbers may not always be taken

as a precursor to betterment of the anemia. Table 5 also shows the average highest reticulocyte count to be 4.9 per cent, and the average day of the highest count to be the eleventh.

TABLE 5.—COMPARATIVE RESULTS OF RETICULOCYTE ESTIMATIONS.

Reticulocyte counts.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemor- rhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Total cases	18	7	8	33
Cases showing increased counts	10	7	7	24
Cases improved, showing increased counts	2	7	6	15
Cases unimproved showing increased counts	8	0	1	9
Average per cent increase	4.5%	6.3%	4%	4.9%
Average day of highest count	10.1	10.6	14	11.3

TABLE 6.—THE EFFECT OF MACROCYTOSIS OF THE ERYTHROCYTES ON THE COURSE OF ANEMIA.

Cell-size estimations.	Group I. Anemia secondary to systemic disease, 23 cases.	Group II. Anemia secondary to hemor- rhage, 14 cases.	Group III. Anemia cause unknown, 13 cases.	Totals.
Total cases	22	14	13	49
Cases showing initial macrocytosis	2	8	3	13
Cases improved showing initial macrocytosis	1	8	3	12
Cases unimproved showing initial macrocytosis	1	0	0	1

The average diameter of the erythrocytes was estimated in every case of the series but one. Table 6 presents a correlation between macrocytosis of the red corpuscles and the course of the anemia for each of the three groups of cases and for the total of 49 cases. It has been noted that in posthemorrhagic anemias there is a tendency toward macrocytosis of the red cells,¹¹ particularly if the anemia is pronounced. This is well shown in Tables 2 and 6 by the fact that over one-half the cases of this group showed an average red cell diameter of 8 μ or over in the dried film, which is above the normal.⁸ In 13 cases of the whole series in which a macrocytosis was present before treatment, 12 showed improvement under therapy, and in 6 the improvement was marked. Eight of the cases successfully treated were in the group of anemias due to hemorrhage. The single patient whose blood did not improve was an old Japanese with a definite pellagra, advanced pulmonary

tuberculosis, and an empyema, who died 2 days after the liver and iron therapy was stopped.

It is evident that red cell macrocytosis indicated that liver and iron therapy would be successful in this small series of 13 cases. Eighteen other cases with erythrocytes of normal average diameter also improved, but in all but 2 of these the anemias were not sufficiently severe to have ordinarily been associated with macrocytosis. It seems then that in a study of a severe anemia the most important indication as to successful iron and liver therapy may be obtained from estimating the average mean diameter of the red cells, and that if this is above the average normal, the anemia is very likely to be benefited. This is comparable to the beneficial effects obtained in Addison-Biermer anemia by feeding liver, as the cases with a high average of large erythrocytes usually respond the best.

Conclusion. In a series of 50 cases of secondary anemia a secondary anemia liver extract combined with iron in a dosage of 12 gm. daily was followed by uniformly good results in all but 1 of 14 cases of posthemorrhagic anemia, while no marked improvement was obtained in 36 cases of anemia due to other causes, except in two instances in which the etiology was undetermined and might have been previous hemorrhage. The improvement in the group of anemias due to bleeding, the majority of which were chronic, seemed more pronounced than with other modes of therapy, and represented the same excellent hematopoietic response in human beings that Whipple produced in dogs on the same type of treatment.

Although 16 other cases of anemia improved moderately while taking the liver extract and iron treatment, some might have improved to the same degree without any treatment, and certainly others might have done as well on large doses of iron alone. A moderate increase in reticulocytes occurred in 24 cases, but as the red blood count increased in less than two-thirds of this number, their presence cannot necessarily be taken as a good prognostic sign. On the other hand, if a macrocytosis of the erythrocytes is present in a case of severe anemia a good response to liver and iron therapy may be expected.

If any conclusions can be drawn from this series of 50 cases, it seems justifiable to recommend the use of the combination of secondary anemia liver extract and iron primarily for anemias due to hemorrhage and for anemia of obscure etiology with macrocytosis of the red blood cells. It may also be of value in other secondary anemias, but at present there are insufficient data available to show whether it should take precedence over large doses of iron alone.

BIBLIOGRAPHY.

1. Whipple, G. H., Robscheit-Robbins, F. S., and Walden, G. B.: *AM. J. MED. SCI.*, 1930, 179, 628.
2. Powers, J. H., and Murphy, W. F.: *J. Am. Med. Assn.*, 1931, 96, 504.
VOL. 184, NO. 3.—SEPTEMBER, 1932 12

3. Wahlberg, J.: *Finska läk-sällsk. handl.*, 1930, 72, 511.
4. Witts, L. J.: *Guy's Hosp. Rep.*, 1930, 80, 253.
5. Keefer, C. S., Yang, Chi Shih, and Huang, K. K.: *Arch. Int. Med.*, 1931, 47, 436.
6. Wyckoff, H. A.: *Personal Communication* (unpublished).
7. Price-Jones, C.: *J. Path. and Bacteriol.*, 1929, 32, 479.
8. Cheney, G.: *Calif. and West. Med.*, 1931, 34, 40.
9. Meulengracht, E.: *Acta med. Scandinav.*, 1923, 58, 594.
10. Minot, G. H., Murphy, W. P., and Stetson, R. P.: *AM. J. MED. SCI.*, 1928, 175, 581.
11. Von Boros, J.: *Wien. Arch. f. inn. Med.*, 1926, 12, 243.

A STUDY ON THE RESULTS OF 1500 BLOOD TRANSFUSIONS IN 1000 CASES.

BY S. H. POLAYES, PH.B., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY AND ASSOCIATE PATHOLOGIST,

AND

M. MORRISON, M.D.,

INSTRUCTOR IN PATHOLOGY, AND ASSOCIATE PATHOLOGIST,
BROOKLYN, N. Y.

(From Department of Pathology, Jewish Hospital of Brooklyn, Dr. Max Lederer,
Director, and the Long Island College of Medicine.)

THE current literature, too extensive to review here, is replete with reports of excellent results obtained by blood transfusion in various diseases. In fact, this mode of therapy seems to have become a panacea for all ailments. However, one who has performed a considerable number of transfusions, and has studied the results obtained, becomes somewhat skeptical about the universal value ascribed to this procedure. We have, therefore, analyzed the results obtained from 1500 blood transfusions performed on 1000 patients who were suffering from various diseases.

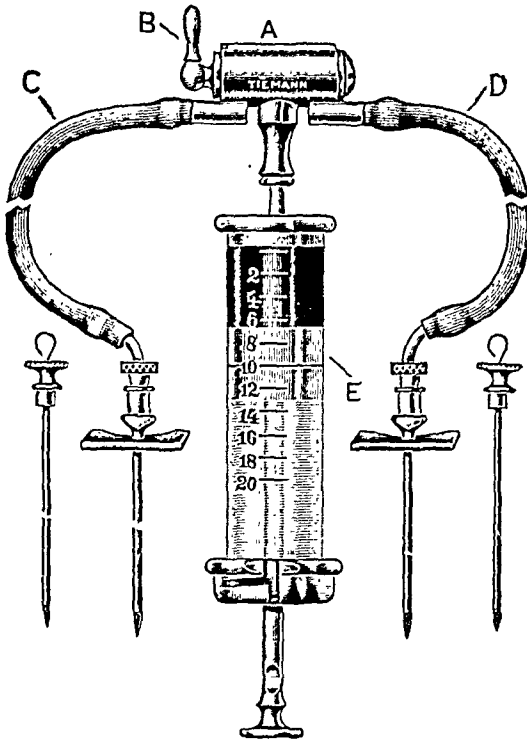
Technique. The group of the patient was determined and the patient's blood was cross-matched with the blood of an homologous donor preceding each transfusion, including repeated transfusions in the same case. Unmodified whole blood was transfused in every instance.

Lederer's* modified Miller apparatus (see illustration) was employed in all cases and was found to be simple and satisfactory. A 20-cc. Luer syringe was used in transfusions for adults and a 10-cc. Luer syringe for children. Normal saline was used to cleanse the syringes and apparatus to insure patency of the system. An 18-gauge Kaliski needle was used for adults and a 20-gauge for children. Hypodermic needles were occasionally employed in cases of small transfusions in very young infants in whom incision for a vein is extremely undesirable. For the donor a 15-gauge Kaliski needle was found most satisfactory. An ordinary muslin bandage, twice

* For a detailed description of the technique employed with this apparatus, the reader is referred to a paper by Dr. Lederer in the *J. Surg., Gynec. and Obst.*, 1923, 37, 221.

wound around the donor's arm supplied adequate constriction when properly adjusted.

The transfusion was, as a rule, performed in the patient's room, with the patient in bed instead of on an operating table, and the donor seated at the bedside. Since it is not necessary to fix the apparatus to any stationary object, the entire outfit was found to be less cumbersome than in most of the other methods described. As a result, the patient usually sensed the simplicity of the procedure, which helped to eliminate the psychic element of fear. In performing transfusions on children and irrational adults, however, it was found necessary to fix the patient's arm by strapping it to a projecting armpiece of a board especially constructed for this purpose, and placed beneath the patient. Such a support can be readily improvised. In these instances, of course, a nurse and an assistant are indispensable. In all other cases, however, one can perform the transfusion unassisted.



It was never found necessary to incise the donor's arm for a vein, and very rarely in adults or older children. Incision had to be resorted to in about 20 per cent of the cases of infants and very young children with collapsed and very small veins.

The dosage varied in each case, depending upon several factors, namely, the age of the patient, the degree of anemia, the cardiac, pulmonary and renal condition as well as the reaction of the patient during the transfusion. Infants and young children received from 50 to 200 cc. of blood, depending on the weight of the child, the general rule being about 20 cc. of blood per kilogram of body weight. Older children received about 150 to 300 cc., the exact amount being determined by the various factors mentioned above in each individual case. The average dose for adults was about 500 cc., although in some instances only 250 cc., while in others as much as 1000 cc. was given. The average time for the administration of 500 cc. of blood was about 20 minutes. In some cases of severe hemorrhage, however, about 1000 cc. were injected in less than 10 minutes in order to counteract rapid loss of blood.

We are cognizant of the fact that in the absence of controls it is frequently very difficult to determine when a blood transfusion is beneficial or not, because the criteria for estimating the value derived from any therapeutic procedure, such as a blood transfusion are not well defined. Thus, a patient may feel symptomatically better or worse following a transfusion and yet the changes noted may be due, not to the transfusion, but to other influences, legion in number. This is especially true in chronic diseases, where, regardless of the therapy employed, the patient is apt to be in a better condition at one time than at another.

On the other hand, there are instances when the part which blood transfusion plays in improving the condition of the patient can be better estimated. Thus, many diseases with severe anemia are known to be alleviated by administration of blood. In some instances, as in cases of pernicious anemia treated with liver, transfusion of blood is of definite aid in the treatment and may be considered of "adjuvant" beneficial effect.

Then again, the beneficial effect of transfusion is obvious in certain cases of persistent bleeding where a blood transfusion sometimes produces hemostasis after all other measures have failed. In occasional instances it is even a life-saving procedure by virtue of replacement of blood. Thus, in shock resulting from extensive hemorrhages, such as those due to trauma, impending death may be combated only by blood transfusion.

Reactions such as those due to blood incompatibility, etc., must be considered harmful effects of transfusion and sometimes, even contributory to death.

TABLE 1.—THERAPEUTIC EFFECT OF BLOOD TRANSFUSION IN 1000 CASES.

Group.	General Summary.				
	Beneficial.		Harmful.		Questionable.
	Life-saving.	Adjuvant.	Unfavorable response.	Contributory to death.	
Number of cases	14	232	28	9	717
Per cent	1.4	23.2	2.8	0.9*	71.7

* In some of these cases the patient was dying, and transfusion was merely a final heroic measure (see Table 4).

Discussion of General Results. Facts no less obvious than those mentioned above have guided the writers in classifying the results of the 1500 transfusions, as shown in Table 1. When there was any doubt as to whether the transfusion was beneficial or not the case was placed in the "questionable" group. From a study of Table 1, it is apparent that in 71.7 per cent of the cases blood transfusion yielded either questionable results or results which were neither beneficial nor harmful. This is in striking contrast to the results reported by the British Red Cross,¹ which in a study of 1215 transfusions found: Good or very good results in 57 per cent,

satisfactory results in 22 per cent, improvement followed by death in 14 per cent and no apparent result in 7 per cent.

In contrast to this, the high percentage of cases in the "questionable" group of the series here reported may be explained by the fact that the indications for the transfusion performed in many of these cases were not strictly medical. Thus, many of them were merely heroic measures to satisfy the family that everything possible had been done for the patient.

In 23.2 per cent of the cases the patients derived some benefit from the transfusions, although whatever improvement was noted could not be ascribed to the transfusion alone, hence they are designated in the table as of "adjuvant beneficial effect." In 2.8 per cent of the cases the patients reacted unfavorably to the transfusions with no subsequent improvement to compensate for the unfavorable reaction. In this group are included those who manifested untoward symptoms indicating disturbances in one or more of the following systems:

1. *Cardiovascular and Vasomotor.* The patient suddenly developed a rapid and irregular pulse, which became imperceptible and which was accompanied by marked dyspnea, orthopnea, cyanosis and extreme weakness. The vasomotor disturbances which frequently followed were evidenced by cold and clammy perspiration, marked pallor, sensation of hot flashes or chills.

2. *Respiratory.* During the transfusion or soon after the patient developed a dry, hacking cough, which at times was accompanied by pain in the chest and even hemoptysis. These symptoms sometimes persisted for a number of hours after the transfusion.

3. *Gastrointestinal.* Abdominal cramps rapidly followed by nausea and vomiting occasionally occurred during or following the transfusion. Occasionally, the vomiting was projectile in character and persisted for 48 hours.

4. *Genitourinary.* Suppression of urine varying in degree from moderate oliguria to complete anuria was another of the reactions encountered. Hematuria occurred rarely.

5. *Nervous.* Patients sometimes complained of severe headache, dizziness and a pounding sensation in the head for hours after the blood transfusion. More alarming reactions, however, were also encountered, consisting of syncope, convulsive seizures, stupor, nystagmus, transitory hemiplegia, or symptoms indicating cerebral hemorrhage or cerebral embolus.

An heterogeneous group of harmful effects may be added which consisted of the following: Thermic disturbances, *i. e.*, hyperpyrexia followed by chills; allergic reactions with or without urticarial skin eruptions; incompatibility reactions with all the phenomena of intravascular agglutination or hemolysis of blood; thrombophlebitis; aggravation of hemorrhagic tendencies in blood diseases, such as leukemia and thrombocytopenia; and last, but not least, the transmission of diseases, such as syphilis, malaria and others.

The causes of the reactions cannot be considered here. For a discussion of this subject, the reader is referred to a paper in press dealing specifically with this phase of the problem.²

TABLE 2.—CASES IN WHICH TRANSFUSION WAS A LIFE-SAVING MEASURE.

Case No.	Diagnosis.	Comment.
131	Lobular pneumonia	Female, aged 8 years. Condition grave. Temperature between 103° and 106°. Following exsanguination of 300 cc. of blood, 150 cc. transfused. Showed a strikingly rapid clinical improvement and temperature declined rapidly to normal.
295	Severe secondary anemia from excessive Roentgen ray and radium therapy	Male, aged 64 years, was helpless before each transfusion and within 24 hours after transfusion, returned to fairly active life. This man's life was prolonged by blood transfusions for a period of 3 years.
363	Lederer's anemia (acute hemolytic anemia)	Male, aged 3 years. Before transfusion, the anemia was rapidly progressive. The red cell count was 1,070,000 prior to, and 2,120,000 within 24 hours after transfusion, the number rapidly increasing to 4,020,000 within 12 days.
958	Lederer's anemia	Male, aged 16 months. Before transfusion he had only 900,000 red cells per c.mm. and appeared to be dying of anemia. A transfusion of only 120 cc. of blood had an immediate beneficial effect, after which the red cell count rapidly returned to normal.
177	Carcinoma of stomach	Male, aged 64 years. Lapsed into a state of shock from severe hematemesis of 1000 cc. of blood. Patient improved immediately after a blood transfusion of 500 cc.
986	Tonsillectomy, postoperative hemorrhage	Male, aged 25 years. Following a tonsillectomy, bleeding from the wound continued. No hemostatic measures proved effective and the patient was dying of hemorrhage. After a transfusion of 500 cc. of blood, the hemorrhage ceased almost at once.
164	Mastectomy for cystic degeneration of breast postoperative hemorrhage	Female, aged 39 years. Suddenly went into a state of shock from a postoperative hemorrhage. Improved immediately after a transfusion of 500 cc. of blood.
984	Amputation of toe, postoperative hemorrhage	Male, aged 22 years. Soon after amputation of toe, lost about a liter of blood from the wound, and lapsed into a state of shock. A transfusion of 600 cc. of blood relieved shock.
580	Hemorrhage following perineorrhaphy	Female, aged 38 years. Soon after operation she presented a picture of impending death due to shock from hemorrhage. She improved immediately after a transfusion of 500 cc. of blood.
870	Hemorrhage following perineorrhaphy	Female, aged 33 years. Shock from hemorrhage was immediately relieved after a transfusion of 500 cc. of blood.

Case No.	Diagnosis.	Comment.
640	Hemorrhage following oöphorectomy for large ovarian cyst	Female, aged 29 years. Shock from post-operative hemorrhage was immediately relieved after a blood transfusion of 750 cc.
810	Postpartum hemorrhage	Female, aged 25 years, with nephritic toxemia developed a severe postpartum hemorrhage and shock. A blood transfusion of 800 cc. immediately relieved the shock.
799	Placenta previa, postpartum hemorrhage	Female, aged 24 years. Shock from severe postpartum hemorrhage immediately relieved after a blood transfusion of 500 cc.
895	Ruptured ectopic, hemorrhage, shock	Female, aged 33 years. The rupture of the Fallopian tube was accompanied by a severe hemorrhage and shock which was relieved after a transfusion of 500 cc. of blood.

Discussion of the Cases in Which Transfusion Was a Life-saving Procedure. A study of Table 2 shows that the majority of cases in which transfusion was a life-saving procedure were those in which there was a rapid loss of a large volume of blood. Thus, in 9 out of the entire 14 cases the condition was one of shock from hemorrhage. The great value of blood transfusions in these cases is, of course, known to all and has been reiterated recently by numerous observers.³⁻¹³ It is of significance to note that 6 of these 9 cases were either obstetrical or gynecologic complications. The inestimable value of blood transfusion in these complications has been emphasized in the recent literature.¹⁴⁻¹⁸

But the life-saving effect of transfusion apparently does not reside in the mere replacement of blood in all cases. Thus, in Case 131 it seems to have hastened the crisis in pneumonia and in Case 986 it proved to be the only effective hemostatic agent to combat what appeared to be fatal hemorrhage, after all other methods were found to be of no avail. Lindquist¹⁹ reports an almost identical case of uncontrollable bleeding from the umbilical cord of an infant. Various hemostatic measures were tried for 6 days without avail. Then 25 cc. of mother's blood was injected into the longitudinal sinus and the bleeding stopped immediately.

The value of blood transfusion in the cases of Lederer's²⁰ anemia deserves special mention. Lederer's original observation, that transfusion acts almost as a specific in this disease, has been confirmed in his cases of this series, as well as in 5 subsequent ones which are not included in this study. Similar reports of the life-saving effect of blood transfusion in cases of Lederer's anemia have been reported by European writers.^{21,22} The patient, usually a child, with evidences of a rapidly developing hemolytic anemia, which appears to be leading to a fatal termination, makes an uneventful recovery very quickly after a blood transfusion.

TABLE 3.—CASES BENEFITED BY TRANSFUSION.
(*Exclusive of Cases in Table 2.*)

Group.	Diagnosis.	Cases transfused.	Cases benefited.	Per cent.
Hemorrhage	Hemophilia	6	5	83.3
	Thrombocytopenia	8	1	12.5
	Epistaxis	6	4	66.6
	Gastric and duodenal ulcer	38	17	44.7
	Ectopic gestation	13	5	37.6
Anemia	Pernicious anemia	29	13	44.8
	Secondary anemia	207	67	32.3
	Leukemia	32	9	28.1
	Ulcerative colitis	12	8	66.6
	Mastoiditis	17	5	29.4
Infection	Peritonitis	12	3	25.0
	Pneumonia (lobar and broncho)	108	25	23.1
	Subacute bacterial endocarditis	18	4	22.2
	Erysipelas	9	2	22.2
	Sepsis (miscellaneous)	207	31	10.1
Miscellaneous diseases	Shock of difficult labor	4	2	50.0
	Intestinal intoxication in children	35	17	48.5
	Surgical shock	44	12	27.2
	Uremia	9	2	22.2

Discussion of Definitely Benefited Cases. In Table 3 an attempt has been made to classify into disease groups those cases in which transfusion was definitely beneficial. (It does not include the cases mentioned in Table 1.) The total number that had received blood transfusions, the number of cases in which the transfusion proved to be definitely beneficial and the percentage of cases benefited are recorded for each disease. The conditions for which the greatest number of cases received transfusion were those of secondary anemia, sepsis, pneumonia, surgical shock, bleeding gastric or duodenal ulcers, intestinal intoxication in children, leukemia and pernicious anemia. The number of cases of other conditions studied in this series is too small from which to draw any definite conclusions as to the value of blood transfusion. For a rough estimate, however, the percentage benefited in these instances will also be found in Table 1.

It will be noted that the greatest percentages of cases in which transfusion proved to be of definite value were found in the following groups, in order of importance: Intestinal intoxication in infants, pernicious anemia, bleeding gastric or duodenal ulcer, including cases during massive bleeding; secondary anemias, due to miscellaneous causes; leukemia, surgical shock and pneumonia. In this study the percentage of cases of intestinal intoxication benefited by transfusion compare favorably with that found by Browne,²³ Robertson,²⁴ Sidbury,²⁵ Moore²⁶ and many other writers.

In the group of patients with pernicious anemia blood transfusion stimulated remissions and alleviated many of the unpleasant symp-

toms. In some of these instances, and also in cases of severe secondary anemia, transfusion may prolong life for years, as exemplified by Case 295 of Table 2.²⁷ Jones²⁸ and Yates²⁹ have reported similar cases. In some instances liver diet and iron or arsenic are insufficient to cause a remission unless supplemented by blood transfusion which stimulates the bone marrow, or which keeps the patient alive until there is a response to the liver therapy, as pointed out by Goodall,³⁰ Manson-Bahr³¹ and Don.³² There is absolutely no danger in transfusing patients with actively bleeding gastric or duodenal ulcers. In no instance of this series did the rise in blood pressure due to the transfusion renew active bleeding.³³ In reviewing the recent literature, one finds that the old fear of causing renewed bleeding or dislodging a thrombus in a vessel by transfusion of a large amount of blood is entirely unwarranted. Bernheim³⁴ found it safe to give about 400 cc. when the blood pressure reached 70 mm. Out of 121 cases of gastric and duodenal hemorrhage Keynes³⁵ obtained good results in 103 and no change in 18 cases. Johansson³⁶ obtained favorable results in 71 per cent of 28 cases of bleeding gastric ulcer. Similar observations were made by Hesse,³⁷ Rausche,³⁸ Plehn,³⁹ Bastedo⁴⁰ and others. Kordenat⁴¹ found that an increase of blood pressure from 108 to 190 and from 130 to 230 mm. did not materially disturb a clot in a small branch of the femoral artery of a dog. In his cases of bleeding gastric ulcer transfusions of 750 cc. of blood stopped the hemorrhage in each instance.

In leukemia the beneficial effects were only transitory, the improvement undoubtedly being due to the improvement of the anemia. Septic conditions for which many have advocated blood transfusion as treatment *par excellence*⁴²⁻⁵⁶ have been benefited but little and patients with bacteremia, not at all.

As for the value of transfusion in surgical shock, in the opinion of the writers, not enough blood was given in most cases of this series. This may account for the lower percentage of cases benefited as compared to the experiences of other observers.^{5,7-13}

The percentage of cases of pneumonia in this series benefited by blood transfusion is small in comparison to that reported by other writers.^{57,58,59} It is possible that the more favorable results found by others may be explained by a more careful selection of cases, as, for example, incipient pneumonias or those with mere congestive changes.

Discussion of Doubtful Cases. In Table 4 the effects in most of the cases cannot be satisfactorily correlated to the end results. Certain it is, however, that in none of them was death expected to occur as soon as it did. The least that can be said is that the transfusion may have been a contributing factor to the cause of the exodus in each of these cases. In Cases 683 and 796 the patients appeared to be in too poor a condition to withstand the strain of a

procedure even less disturbing than a blood transfusion. Cases 763 and 843 died of what appears to the writers to have been due to a condition of right heart overloading. Case 888 probably died of a cerebral embolus, the origin of which could not be determined. Case 606 died of a cerebral hemorrhage. This type of case deserves special emphasis. Individuals with aplastic anemias should be transfused with the greatest of caution because of the vulnerability of their vessel walls. Hemorrhages are prone to occur with the least amount of added strain to the vessels. Small transfusions given very slowly should be the rule in these cases.

TABLE 4.—CASES IN WHICH TRANSFUSION WAS CONTRIBUTORY TO DEATH.

Case No.	Diagnosis.	Age.	Comment.
608	Pneumonia	2½ mos.	Died a few minutes after transfusion of 70 cc. of blood.
642	Uremia	15 yrs.	Sudden unexpected death occurred 12 hours after transfusion. The patient's condition was made definitely worse by the transfusion of 350 cc. of blood.
665	Pneumonia with empyema	6 yrs.	Immediately after transfusion of 150 cc. of blood, there was a sudden drop in temperature from 105° to 99°, accompanied by fatal shock.
683	Bleeding gastric ulcer	61 yrs.	The patient was in very poor condition and ceased to breathe during the transfusion.
763	Carcinoma of rectum	65 yrs.	Died during transfusion after having received 700 cc.
796	Leukemia (chronic myeloid)	48 yrs.	Died 10 minutes after a blood transfusion of 350 cc. The patient was not expected to die so suddenly.
843	Suppurative cholangitis, stone in common duct	36 yrs.	There was a rapid rise in temperature from 99° to 108° with associated signs and symptoms of cardiac dilatation.
888	Bronchopneumonia second degree burn	3 mos.	The clinical picture suggested an embolus causing sudden death after 80 cc. of blood were administered. The heart continued to beat for 20 minutes after cessation of respiration.
606	Aplastic anemia	24 yrs.	The patient received 750 cc. of blood. She soon developed cerebral complications indicating a cerebral hemorrhage and died very soon after.

Conclusions. 1. Of 1000 cases receiving a total of 1500 blood transfusions the results were either of doubtful benefit or of no effect whatever in 71.7 per cent.

2. Blood transfusion proved to be a life-saving procedure in 1.4 per cent of the cases. Most of these were patients who suffered a sudden loss of a large quantity of blood.

3. Some definite adjuvant beneficial effects were derived from transfusion in 23.3 per cent of the cases.

4. The reaction to the transfusion was unfavorable and the results harmful in 3.7 per cent of the cases.

5. The transfusion was apparently contributory to death in 0.9 per cent of the cases.

6. The excellent results from blood transfusion in the wide variety of diseases as reported by other writers could not be obtained in this investigation. Definitely beneficial results should be expected only in the type of case indicated in this study.

REFERENCES.

1. Report Brit. Red Cross: J. Am. Med. Assn., 1929, 92, 485.
2. Polayes, S. H., and Lederer, M.: J. Lab. and Clin. Med. (in press).
3. Kuttner: J. Am. Med. Assn., 1924, 83, 209.
4. Blain, A. W., and Brines, O. H.: Arch. Surg., 1926, 12, 140.
5. Carlton, C. H.: Lancet, 1926, 2, 850.
6. Andresen, A. F. R.: J. Am. Med. Assn., 1927, 89, 1397.
7. Vosburgh, C. H.: J. Am. Med. Assn., 1927, 89, 319.
8. Stofer, D. D.: Ann. Int. Med., 1927, 1, 442.
9. Lahey, F.: J. Am. Med. Assn., 1927, 89, 1735.
10. Crile, G. W., and Higgins, C. C.: J. Am. Med. Assn., 1927, 89, 1738.
11. Keith, N. M.: J. Am. Med. Assn., 1929, 93, 1517.
12. Robertsons, O. H.: Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions, Nos. 1-7. Special Report Series 25. Wound Shock and Hemorrhage, Medical Research Committee, Oxford, 1919.
13. Atchley, D. W.: J. Am. Med. Assn., 1930, 95, 385.
14. Schweitzer, B.: München. med. Wehnschr., 1921, 68, 699.
15. Goder: Deutsch. Ztschr. f. Chir., 1922, 170, 384.
16. Schafer, P.: Ztschr. f. Geburtsh. u. Gynäk., 1923, 85, 607.
17. Ward, G. G.: Wisconsin Med. J., 1925, 23, 489.
18. Ward, G. G.: Illinois Med. J., 1926, 69, 101.
19. Lindquist, E.: Zentralbl. f. Gynäk., 1928, 52, 961.
20. Lederer, M.: Am. J. Med. Sci., 1925, 170, 500; 1930, 179, 228.
21. Holst, P. F.: Acta med. scand., 1928, 68-Suppl. pp. 23, 27, 469.
22. Christiansen, T.: Hospitalstidende, 1929, 72, 7, 178.
23. Browne, A.: Illinois Med. J., 1925, 48, 363.
24. Robertson, B., Brown, A. V., and Simpson, R.: Northwest Med., 1921, 20, 233.
25. Sidbury, J. B.: J. Am. Med. Assn., 1927, 89, 855.
26. Moore, C. U.: Northwest Med., 1928, 27, 140.
27. Polayes, S. H., and Lederer, M.: J. Am. Med. Assn., 1930, 95, 407.
28. Jones, H. W.: J. Am. Med. Assn., 1926, 86, 1673.
29. Yates, J. L., and Thalheimer, W.: J. Am. Med. Assn., 1926, 87, 2156.
30. Goodall, A., and Calder, A. M.: Lancet, 1929, 2, 1144.
31. Manson-Bahr, P. H.: J. Trop. Med., 1929, 32, 42.
32. Don, C. S.: Brit. Med. J., 1930, 2, 280.
33. Polayes, S. H., Gray, I., and Friedman, B.: Am. J. Surg. (in press).
34. Bernheim, B. M.: Blood Transfusion, Hemorrhage and the Anemias, Philadelphia, J. B. Lippincott Company, 1917.
35. Keynes, G.: Brit. Med. J., 1926, 8, 980.
36. Johansson, S.: Hygiea, Stockholm, 1929, 91, 209.
37. Hesse, E.: Deutsch. med. Wehnschr., 1926, 52, 620.
38. Rausche, C.: Deutsch. med. Wehnschr., 1926, 52, 1428.
39. Plehn, A.: Deutsch. med. Wehnschr., 1926, 52, 1120.
40. Bastedo, W. A.: New York State J. Med., 1927, 27, 290.
41. Kordenat, R. A.: Mil. Surgeon, 1930, 66, 206 or 376.
42. Unger, L. J.: J. Am. Med. Assn., 1922, 78, 1418.
43. Hansen, R. R.: Iowa State Med. Soc. J., 1925, 15, 124.
44. Baranger, J.: Paris méd., 1925, 55, 251.
45. Howell, K., et al.: J. Inf. Dis., 1926, 39, 1.
46. Neff, F. C.: Southern Med. J., 1926, 20, 519.

47. Caplesco, Poenaru: Bull. de l'Acad. de méd., 1926, 95, 17.
48. Wiethe, C.: Arch. f. klin. Chir., 1926, 140, 189.
49. Stetson, R. E.: Am. J. Med. Sci., 1924, 168, 534.
50. Reimold, W., and Kramer, B.: Klin. Wehnschr., 1927, 6, 305.
51. Gittings, J. C.: J. Am. Med. Assn., 1927, 89, 861.
52. Rockwell, O. E.: J. Med., 1928, 8, 588.
53. Hoche, O.: Wien. klin. Wehnschr., 1928, 41, 344.
54. Bertocchi, A.: Policlinico, 1929, 36, 549.
55. Działoszynski, A.: Med. Klin., 1930, 26, 11.
56. Kordenat, R. A.: Illinois Med. J., 1930, 57, 132.
57. Wilbert, C. D.: J. Am. Med. Assn., 1927, 89, 861.
58. Flinn, L. B.: Am. J. Dis. Child., 1929, 37, 596.
59. Krahulík, L., and Koch, L. A.: Am. J. Dis. Child., 1930, 39, 34.

DIFFERENTIAL ARTERIAL TENSION.

By EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, RUSH MEDICAL COLLEGE, UNIVERSITY
OF CHICAGO,

AND

DUANE W. PROPST, A.B., B.S., M.D.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF ILLINOIS, COLLEGE OF MEDICINE,
CHICAGO, ILL.

THE term differential pressure has been applied by Cyriax^{1,2} to differences in readings of the arterial tension on the two sides of the body. Such asymmetry of the arterial tension may be of little clinical importance in some instances, whereas in other cases the asymmetry may be most significant.³ Relatively little attention has been given to this interesting phenomenon. Extensive studies⁴ of the difference in arterial tension in the arms as contrasted to the legs have revealed that the arteries in the leg bear pressures markedly higher than those in the arms; the pressure changes in a given limb which accompany a change of position may be largely accounted for by hydrostatic pressure changes.⁴ Higher tension in the arms than in the legs is characteristic of coarctation of the aorta³⁻⁵ An arteriovenous aneurysm in an extremity markedly lowers the arterial tension of that extremity.⁶ The reputed significance of asymmetry of the arterial tension in pulmonary tuberculosis is very doubtful and probably invalid.⁷

Relatively meager data are available regarding the incidence of asymmetry of the arterial tension.⁸ To determine this point the arterial tension was measured in both arms in a series of 600 individuals. The cases were derived from private patients, dispensary patients and applicants for life insurance. No children are included in the group, the ages ranging from 18 to 60 years. For purposes of definition and tabulation we have declared asymmetry to exist whenever the difference in systolic tension is 10 mm. Hg or greater or when the diastolic difference is 5 mm. Hg or greater. All deter-

minations were made with mercury manometers. Repeated readings on the right, left and again on the right were made in all instances of asymmetry to rule out errors due to fluctuation of the general tension from emotional or other causes. It is believed, therefore, that asymmetry under such conditions represents a significant pressure difference in the 2 arms. The results of these observations are best presented in tabular form:

TABLE 1.—SUMMARY OF BLOOD PRESSURE OBSERVATIONS ON 600 CASES.

	No. cases.	Per cent.
Total number cases	600	
Males	415	69
Females	185	31
Cases with normal arterial tension	466	77
Cases with high arterial tension	127	22
Cases with low arterial tension	7	1
Asymmetric cases	94	15.7 (% of total)
Asymmetric persistent in	75	80 (% of asymmetric cases)
Asymmetric males	69	74
Asymmetric females	25	26
Cases with normal arterial tension	59	60
Cases with high arterial tension	34	35
Cases with low arterial tension	6	5
Systolic highest on right	18	19
Systolic highest on left	11	12
Diastolic highest on right	30	32
Diastolic highest on left	18	19
Both systolic and diastolic highest on right	18	19
Both systolic and diastolic highest on left	4	5
Systolic high right, diastolic on left	2	2.5

The incidence of asymmetry in the present group of 600 individuals was slightly over 15 per cent. This is of similar magnitude to that reported by Kay and Gardner,⁸ who found 20 per cent of asymmetry in a group of 125 patients. Bodenstab⁹ reports far greater frequency in a short series, but his criteria of asymmetry included differences as low as 2 mm. In view of the normal physiologic fluctuation of the arterial tension,¹⁰ such minor variations must be considered insignificant. It has long been assumed and taught that asymmetry of the arterial tension is most rare and unusual, being limited to a few cases of aortic aneurysm or trauma; such is clearly not the case.

Asymmetry does not appear more frequently in either sex. Asymmetry, however, is definitely more frequent in instances of hypertensive arterial disease than in those with arterial tension at normal levels. The instances of true hypotension were too few to warrant the drawing of conclusions.

There appears to be a slightly greater frequency of elevation of either the systolic or diastolic or both on the right side, but this is by no means marked. It has been noted in a number of instances, observed repeatedly, that when the arterial tension approached nor-

mal levels the asymmetry tended to diminish or disappear. This was true in both hypertensive and hypotensive patients. Systolic and diastolic asymmetry appear with almost equal frequency.

Physiologic explanation of the asymmetry was largely problematical in the majority of cases. Aortitis was observed three times, tabes twice. In a number of instances atheromatous patches at the orifice of the subclavian artery were suspected, although unproven.³ The instance associated with cervical ribs was most instructive. In 3 persons injury to one arm with atrophy from disuse was associated with reduced tension upon that side, although curiously enough in other patients with injury to one arm asymmetry of the blood pressure was not elicited. A more detailed record of findings in several interesting instances of asymmetric arterial tension follows:

Case Abstracts. CASE 1.—Mr. P. R. S., aged 36 years, married, industrial chemist, was first seen, March 25, 1929, at which time he complained of pain in the region of the left occiput radiating downward to the shoulder. The pain was not affected by motion. The past history revealed an appendectomy in 1922, influenza in 1919 and tonsillitis once per winter. Recently hypertension had been discovered. Physical examination revealed 2 devitalized teeth, chronic pharyngitis, normal pulmonary fields, normal urine and a hemoglobin content of the blood of 74 per cent (Dare). The second aortic sound was accentuated, the cardiac apex was 1 cm. to the left of the midclavicular line. The arterial tension was 172/130 on the right and 145/100 on the left, falling to 130/80 on the right following the inhalation of amyl nitrite.¹¹ The family history revealed hypertensive disease in both parents. The following factors were considered as probably bearing upon the etiologic background of his hypertension: dental infection, hereditary influences, possible renal injury from benzene poisoning (occupation).

On April 3, 1929, the maximum specific gravity of his urine, after 14 to 16 hours' fluid deprivation^{10,12} was 1.020. The arterial tension had fallen to 142/110 on the right under therapy with bismuth subnitrate.^{10,13,14} Pain had disappeared.

On April 17 the arterial tension was 145/110; the maximum specific gravity had risen to 1.024 on repetition of the urinary concentration test.

On October 12 there occurred a sudden recurrence of pain in the left occipital region, radiating to the left shoulder and down the left arm. The reappearance of pain followed, carrying a heavy burden. The arterial tension was: right, 170/130; left, 130/80. Cervical rib was now strongly suspected. Roentgen plates revealed a left cervical rib. (Figs. 1 and 2.)

On October 19 the arterial tension was: right, 170/125; left, 140/102. Pain was much reduced.

On November 9 the tension was much more symmetrical: right, 142/105; left, 134/100; there was no pain. It was noted that the asymmetry of the arterial tension varied directly with the severity of the pain. Surgical intervention was urged because of the persistence of the compensatory hypertension on the side other than the lesion. It was felt that pressure from the cervical rib upon the brachial plexus depressed the arterial tension on the left side and that the systemic hypertension was at least largely compensatory. Spontaneous improvement was not to be anticipated, but exacerbation of the condition in the future was not unlikely. Gangrene of the hand is not uncommon as a result of pressure upon neural and vascu-



FIG. 1.—Case 1. Reduced Roentgen ray photograph showing the broad base of the cervical rib on the left side.



FIG. 2.—Case 1. Retouched reduced Roentgen ray photograph showing the extent of the cartilaginous tip of the cervical rib on the left side.

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lar structures by cervical ribs,^{15,16} although in most instances cervical ribs are essentially asymptomatic.^{17,18,19,20} Cervical ribs with large bases, such as this one, are frequently associated with elongated fibrocartilaginous tips which are not detected by Roentgen ray.²² It has been stated^{21,23} that the surgical indications depend directly on the degree of circulatory disturbance.

On November 23 the patient was operated upon by Dr. R. C. Bourland, of Rockford, Ill. The left cervical rib was found to be in close relationship to the brachial plexus which was wound about the long fibrocartilaginous tip. Pressure upon the plexus was obvious. Removal of the rib was most difficult but was successfully accomplished. Postoperative observations of the arterial tension revealed: November 23: right, 118/90; left, 98/74. November 24: right, 150/108; left, 130/100. November 25: right, 156/130; left, 140/110. November 26: right, 166/120; left, 160/110.

On January 11, 1930, the arterial tension was still somewhat asymmetric (right, 175/110; left, 140/100), although the diastolic asymmetry was much reduced. No arteriosclerosis was demonstrable, the hypertonia being purely spastic, as revealed by the response to the inhalation of amyl nitrite;¹¹ the blood pressure fell to 118/70. Bismuth subnitrate was again advised.

On March 5 the asymmetry had disappeared for the first time. The blood pressure was: right, 150/85; left, 142/86. Throughout the remainder of 1930 and to date in 1931 the readings revealed negligible or no asymmetry.

The above case is illustrative of more than the mere fact that a cervical rib may account for asymmetry of the arterial tension. In a major degree the vasotonic disturbance so engendered may be considered responsible for the patient's hypertension: Pressure on the plexus on the left depressed the tonus of the vessels of the left arm; in order to maintain an adequate circulation a compensatory hypertonia developed in the remainder of the circulation. This compensatory hypertension had persisted for a long but unknown time prior to its discovery. No immediate return to normal could be anticipated following the removal of the rib, for the prolonged hypertonia had undoubtedly created hypertrophy of the medial muscle of the arterioles and the earlier steps in the pathogenesis of hypertensive disease^{10,14} had already occurred. The habit of arteriolar spasticity was present and the vicious circle of spasticity, arteriolar fatigue and hyperirritability was operative.¹⁰ To overcome this "perpetuating factor" in hypertensive disease prolonged arteriolar relaxation and rest are necessary. It is in this connection that bismuth subnitrate has proven of value.^{10,13,14} The above case is illustrative of the necessity for prolonged arteriolar sedation. The arterial tension has slowly returned to normal levels.

CASE 2.—Mrs. R. B., aged 45 years, Para-III. This patient had been under observation for 2 years with migraine and a menopausal type of arterial hypertension. The migraine had been successfully controlled by dietary régime, peptone injections, as suggested by Miller and Raulston,²⁴ and an increase in fluid intake. The arterial tension had been normal for 18 months. On June 27, 1928, the patient complained of pain in the right arm, extending from the wrist to the shoulder, which followed 24 hours after a period of numbness in the arm. Associated with this was a dull cephalalgia. Motion did not affect the pain; no tenderness could be elicited. There had been no recent infection. The nose and throat ap-

peared normal. The arterial tension was: right, 130/70; left, 128/80. The diagnostic impression at that time was neuritis, possible beginning herpes zoster.

No relief was obtained with the administrations of analgesics and acetylsalicylic acid. The distress continued unaltered to July 23, when the patient complained of marked soreness in the muscles of the right arm, with tremor resembling tetany. Roentgen ray of the shoulder revealed no abnormalities. On the advice of another physician a tonsillectomy was performed, November 2, by Dr. Crage, Chicago. One tonsil contained pus. No relief was obtained. On November 16 the patient first noted waves of erythemic redness and swelling of the right hand. Determination of the arterial tension at this time revealed marked asymmetry: right, 90/60; left, 130/70. No explanation of the asymmetry could be found. It was suggested that the patient take ephedrin sulphate, $\frac{3}{4}$ grain, three times per day, in an attempt at increasing the arterial tonus on the affected side. Within a few hours all discomfort ceased. She continued the ephedrin for several days and reported on November 24, at which time the degree of asymmetry of the arterial tension was much reduced: right, 118/70; left, 134/80. There has been no recurrence of pain since then, nor has any appreciable asymmetry been elicited.

In this second case we are at a loss to account for the asymmetry. It is quite certain no cervical ribs, aortic lesion or other gross abnormality existed. The prompt disappearance of the persistent pain upon therapy with the pressor substance ephedrin was most remarkable; it is probable that some ill-defined form of vasomotor palsy in the right arm was responsible for her symptoms.²⁸ After the first examination, in June, the arterial tension was determined only on the left (normal) side to avoid compression of the painful arm. Had bilateral studies been made sooner it is probable that much of the prolonged distress could have been avoided. It is notable that in both cases cited the subjective symptoms were limited to the side with the *lower* arterial tension.

CASE 3.—Mr. W. E. G., aged 56 years, editor by occupation. On July 27, 1931, he first complained of paresthesia and numbness in the left hand and arm and some in the leg on arising in the morning. At times the numbness was associated with transient palsy of the left side. The paresthesia and palsy completely disappeared with activity. His past history was irrelevant to the present complaint. Examination revealed moderate pallor, the patient was tall and slender, of Stillar physique, the cardiac sounds were soft but clear and regular. The arterial tension was asymmetric: right, 118/88; left, 98/64. Urinalysis revealed normal findings. The hemoglobin was 90 per cent (Dare); erythroplastids, 4,520,000.

No thoracic or cerebral lesion could be found to account for the asymmetry. Roentgen ray examination failed to reveal a cervical rib. It was suggested he take $\frac{3}{4}$ grain ephedrin sulphate, once daily, on retiring. This resulted in distinct improvement of the morning numbness on the right side, but caused considerable insomnia. The arterial tension on July 30 was: right, 104/70; left, 102/70. The basal metabolic rate was found to be -25 per cent. Therapy with desiccated thyroid has since resulted in a gain in weight, complete cessation of the asymmetry of the arterial tension and disappearance of his distressing morning paresthesias.

It is characteristic of the symptoms attributable to either actual or relative hypotension¹⁰ to be most notable early in the morning after sleep, at which time the arterial tension is lowest during the waking hours. This last case had a true hypothyroidism, with hypotension; the unexplained asymmetry exaggerated the hypotension on the left side sufficiently to produce subjective symptoms. Moderate hypotonia is usually asymptomatic. The primary mechanism creating the asymmetry is undetermined.

Asymmetry of the arterial tension has distinct clinical significance. It is far more frequent than is generally assumed. Failure to determine the arterial tension on both sides may result in gross diagnostic error, as illustrated in the second case cited. From the point of view of examination for life insurance, asymmetry is of importance, for grave errors are possible. A normal arterial tension on one side does not prove a normal tension on both. It is probable that the majority of instances of asymmetry are essentially transient, unless some definite organic lesion, such as aortitis, cervical rib, atrophy or trophic disturbance exists. But individuals in whom the vasomotor control is unstable are prone to reveal asymmetry of the arterial tension. Although the asymmetry may not be uniformly persistent, it tends to be recurrent. Both hypertonia and asymmetry may be attributed to variability of the vasomotor tone. Asymmetry of the arterial tension is more frequently encountered in patients with hypertensive disease than in those with normal blood pressure. Asymmetric reduction of the arterial tension in an extremity, as in the first case cited, may be a factor in the etiology of systemic hypertensive arterial disease by creating a prolonged compensatory arterial hypertonia. It is only the exceptional case which presents subjective symptoms.

Conclusions. Asymmetry of arterial tension, as defined in this paper, occurs in approximately 15.7 per cent of adults. It is more common in persons with elevated arterial tension and in those with vasomotor instability. Sex is not a factor. Elevation of the systolic and diastolic tension is somewhat more frequent on the right than on the left. Arteriolar spasticity, cervical rib, aortitis, injury to an extremity with atrophy, arteriovenous aneurysm and central trophic disturbances, as occur in tabes dorsalis, are all factors to be considered in evaluating the causation of persistent asymmetry.

REFERENCES.

1. Cyriax, E. F.: *Quart. J. Med.*, 1920, **13**, 148.
2. Cyriax, E. F.: *Quart. J. Med.*, 1921, **14**, 309.
3. Rolleston, Sir H.: *Internat. Clin.*, 1928, **3**, 84.
4. Strang, J. M.: *New England J. Med.*, 1929, **200**, 167.
5. Blumgart, H. L., Laurence, J. S., and Ernstene, A. C.: *Arch. Int. Med.*, 1931, **47**, 806.
6. Smith, C.: *Arch. Int. Med.*, 1931, **48**, 187.
7. Fernandez, C. D., and Gutierrez, R. N.: *Arch. de Cardiol. y Hematol.* (Madrid), 1931, **11**, 257.

8. Kay, W. E., and Gardner, K. D.: *Calif. and Western Med.*, 1925, 33, 578.
9. Bodenshtab, N. H.: *Lancet*, 1925, 45, 360.
10. Stieglitz, E. J.: *Arterial Hypertension*, Hoeber, New York, 1930.
11. Stieglitz, E. J.: *Arch. Int. Med.*, 1930, 46, 227.
12. Fishberg, A. M.: *J. Am. Med. Assn.*, 1927, 88, 2018.
13. Stieglitz, E. J.: *J. Pharm. and Exp. Therap.*, 1927, 32, 23.
14. Stieglitz, E. J.: *J. Am. Med. Assn.*, 1930, 95, 842.
15. Langeron and Desbonnets: *Bull. et mém. de la Soc. nat. de chirur.*, 1931, 57, 704.
16. Telford, E. D., and Stopford, J. S. B.: *Brit. J. Surg.*, 1931, 19, 557.
17. Delahaye, M.: *Bull. et mém. Soc. anat. de Paris*, 1922, 92, 277.
18. Maxwell, J.: *Proc. Royal Soc. Med.*, 1929, 22, 1240.
19. Tretter, H.: *Med. Klin.*, 1925, 25, 1095.
20. Barling, S.: *Brit. J. Child. Dis.*, 1910, 7, 108.
21. Myers, W. A.: *J. Missouri Med. Assn.*, 1924, 21, 146.
22. Miller, J. L.: *Am J. MED. Sci.*, 1911, 142, 811.
23. Adson, A. W., and Coffey, J. R.: *Ann. Surg.*, 1929, 85, 839.
24. Miller, J. L., and Raulston, B. O.: *J. Am. Med. Assn.*, 1923, 81, 1894.
25. Osler, Sir W.: *Proc. Royal Soc. Med.*, London, 1912, 6, 78, *Clin. Sec.*

SOME RACIAL DIFFERENCES IN BLOOD PRESSURES AND MORBIDITY IN A GROUP OF WHITE AND COLORED WORKMEN.

JAMES M. ADAMS, M.D.,

NEW ORLEANS, LA.

AN experience of 11 years as an industrial physician in an industry employing 5074 men between the ages of 18 and 65, approximately one-third of whom were colored and the remainder white, showed some marked differences in physical characteristics and morbidity statistics in the two races. The most striking difference noted on physical examination was in the blood pressure. Accordingly a study was made of 28,221 blood pressure readings covering all of the ages represented in our personnel. There were approximately 14,000 individuals on whom readings were made, 8000 of whom were white and 6000 colored, or an average of two readings for each individual at different ages. Almost all of the whites were native born Americans. All the examinations were made on apparently healthy individuals and were noted on examinations of applicants for employment (9000) and annual health examinations (5000). None were included of individuals who were sick or who consulted us for medical advice. An average of three and four-fifths readings at different ages were made of the 5000 employees represented, or 19,000 readings, and a single reading of the 9000 applicants for employment. The period covered was from 1920 to 1930 inclusive.

Table 1 compares the average systolic and diastolic pressures of the white and colored men by age groups. The distribution into age groups is not equal, two-thirds of the readings having been made on men between the ages of 21 and 35. The numbers in the groups

from 41 to 65 years are too small for computing dependable averages, but are sufficient for comparative study. The average pressures in the group were systolic 124, diastolic 83. The average for the whites was systolic 121, diastolic 81; for the colored, systolic 128, diastolic 85. The average for the colored was therefore 7 mm. higher for the systolic readings, and 4 mm. higher for the diastolic than the average for the whites. This deviation occurred in each age group, the systolic pressure of the colored ranging from 4 to 13 mm. higher than the whites in the different age groups, and the diastolic pressures ranging from 2 to 6 mm. higher.

TABLE 1.—A COMPARISON OF BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Number of cases.			Average systolic pressure.				Average diastolic pressure.			
	White.	Col.	Total.	White.	Col.	*Difference.	Total.	White.	Col.	*Difference.	Total.
18-20	1532	632	2164	117	125	8	119	77	81	4	78
21-25	4751	3680	8431	121	127	6	123	80	82	2	81
26-30	3462	2552	6014	120	126	6	123	80	84	4	83
31-35	2366	1984	4350	121	127	6	123	82	85	3	83
36-40	1550	1373	2923	122	128	6	125	83	87	4	85
41-45	905	644	1549	123	131	8	126	83	89	6	86
46-50	547	470	1017	126	137	11	131	88	92	4	90
51-55	334	405	739	130	134	4	132	90	93	3	92
56-60	250	430	680	126	139	13	134	90	96	6	94
61-65	156	198	354	139	148	9	144	92	96	4	94
Total	15853	12368	28221	121	128	7	124	81	85	4	83

* Millimeters of mercury that the average pressures of the colored men are greater than those of the white men.

Beyond 40 years of age the pressures of the colored men advanced more rapidly than that of the whites. The average systolic pressures of the whites between the ages of 18 and 40 was 120 and that of the colored was 127, a dominance of 7 mm. for the latter. In the group from 41 to 65 years the average was, for the whites 127 and for the colored 137, a dominance of 10 mm. for the latter, or 3 mm. more than in the 18 to 40 group. The diastolic pressures were for the 18 to 40 group, whites, 80; colored 84; difference 4 mm. For the 41 to 65 age group they were whites, 87; colored, 92; difference, 5. The dominance of the pressure of the colored was 1 mm. greater in the second age group than in the first.

Table 2 shows the maximum and minimum pressures in the series by age groups. The maximum pressures of the colored men are higher in practically every age group, and the average of the maximum pressures in all groups shows the colored systolic 17 mm. and the diastolic 4 mm. higher than that of the whites. The maximum systolic pressures in neither race is influenced by age, those of the younger ages being as high as those in the older groups. The highest recorded for a white man was at 24 years of age. The high

pressures in the younger ages were very probably influenced by a psychologic factor more than in the older men, and the pressures in the older men represent a greater amount of damage than in the younger. The average of the minimum pressures is the same in both races for the systolic, and for the diastolic that of the white men is 2 mm. higher than that of the colored. The minimum diastolic pressures for the colored however, cover a wider range than do those for the whites. The ranges are: white, 40 to 52; colored, 30 to 52. This may be accounted for by the fact that damage to the aortic valve and the first portion of the aorta is more common in the colored than in the whites, and occurs at an earlier age in the former race.

TABLE 2.—MAXIMUM AND MINIMUM BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Maximum.				Minimum.			
	Systolic.		Diastolic.		Systolic.		Diastolic.	
	White.	Col.	White.	Col.	White.	Col.	White.	Col.
18-20	180	190	110	128	78	84	40	46
21-25	224	220	138	160	74	80	38	32
26-30	200	210	130	132	74	72	40	30
31-35	210	226	140	142	70	60	50	40
36-40	200	240	140	160	78	80	40	38
41-45	218	224	140	150	80	80	40	42
46-50	200	260	162	148	60	64	42	32
51-55	210	242	164	160	94	96	40	52
56-60	204	204	140	142	96	90	50	50
61-65	200	200	162	150	88	80	52	52
Average	205	222	143	147	79	79	43	41

Table 3 shows the relation of albuminuria to blood pressures by races and age groups. While the percentage showing albumin in the urine is the same for both races, the age distribution and the difference in the two races of the relation of albumin to both the systolic and diastolic pressures is significant. From 18 to 30 years of age the whites show a preponderance of albuminuria, while in the ages 31 to 65 the colored are the most numerous. In the former age group 14 per cent of the whites and 12 per cent of the colored, and in the latter age group 9 per cent of the whites and 13 per cent of the colored had albumin in the urine. The lowest percentage for both races occurred in the ages 31 to 40. The average systolic pressure for the whites with albuminuria was 122, and without albumin was 121, a difference of only 1 mm. of mercury. In the colored group the figures were: with albumin 135, without albumin 128, a difference

TABLE 3.—RELATION OF ALBUMINURIA TO BLOOD PRESSURES OF WHITE AND COLORED MALES BY AGE GROUPS.

Age groups.	Number of cases.				Per cent with albumin.				Average systolic pressure.						Average diastolic pressure.					
	With albumin.		Without albumin.		With albumin.		Without albumin.		With albumin.		Without albumin.		With albumin.		Without albumin.		With albumin.		Without albumin.	
	Col.		Col.		Col.		Col.		Col.		Col.		Col.		Col.		Col.		Col.	
	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.	White.	Col.
18-20	311	100	1221	532	20	16	117	127	120	117	124	119	76	82	77	80	78	80	78	80
21-25	682	457	4069	3223	14	12	121	129	120	121	126	123	80	84	80	82	82	80	81	82
26-30	392	252	3070	2300	11	10	119	131	124	120	126	123	80	87	80	83	83	80	81	83
31-35	167	176	2199	1808	7	9	123	132	128	120	126	123	87	85	81	84	86	81	83	84
36-40	106	129	1444	1244	7	9	144	138	133	122	127	124	86	93	80	83	90	83	84	86
41-45	65	76	840	568	7	12	126	143	135	123	130	125	88	98	81	88	93	81	85	88
46-50	49	89	498	381	10	19	130	150	143	125	133	129	96	100	87	90	98	87	90	88
51-55	57	87	277	318	17	21	135	145	141	129	131	130	95	99	90	91	98	90	90	91
56-60	52	88	198	342	21	20	132	146	141	124	137	132	94	98	89	95	96	89	93	95
61-65	26	46	130	152	17	23	140	152	148	139	146	143	89	97	92	96	94	92	94	96
Total	1907	1500	13946	10868	12	12	122	135	128	121	128	124	82	89	80	85	85	80	83	85

of 7 mm. The diastolic pressures showed the same trend and were as follows:

	Mm.		Mm.
White with albumin	82	Colored with albumin	89
White without albumin	80	Colored without albumin	85
Difference	2	Difference	4

The age distribution and the contrast in the difference between the pressures with and without albuminuria indicate that a larger proportion of the albuminuria in the whites was functional, especially in the younger ages, than in the colored, and conversely that the albuminuria in the colored represented a greater amount of kidney damage than in the whites.

In the same group, complete and reasonably accurate records were kept of the time lost over a period of seven years. Table 4 shows the actual number of cases of sickness, the actual number of days lost and the average duration per case, classified by races and by causes, using the nomenclature of the International Classification of causes of death. Table 5 further analyzes these figures, showing the annual rate per thousand, the average number of days lost per year by each individual, and the percentage of time lost by each disease group as compared with the total, classified in the same manner as in Table 4. In practically all of the cases of illness except malaria, the patients were treated by their own physicians. But all cases were supervised by our medical staff and represent in the main, actual disability and accurate diagnoses.

It is first noted that of the total number of 22,461 cases, 7666 or slightly more than one-third are colored. This is the approximate proportion of colored to white individuals in the group, as is indicated in the case rate of 623 per 1000 for the whites and 651 per 1000 for the colored, the case rate for the group being 632 per 1000. But when we note the average number of days lost per year by each individual, we find a greater difference in the two races. The whites lost an average of 8.05 days per year and the colored 9.79, the average for the group amounting to 8.62 days. The increased amount of time lost by the colored over the whites is due to the longer duration per case of illness of the colored (15 days), than of the whites (12.9 days). The average duration for the group is 13.6 days per case.

The analysis of the causes of disability reveal further racial differences. In the respiratory group, the frequency for the whites is greater, 260 per 1000, as against 194 per 1000 for the colored. The duration per case is, however, greater for the colored, 12.7 days per case as compared with 9.2 days for the whites, resulting in a greater amount of time lost per individual by the colored than by the whites (2.45 days per year by the colored and 2.39 by the whites). Nevertheless, the amount of time lost from these diseases as compared with the total time lost from all causes, is greater for

the whites than for the colored (whites 29.7 per cent and colored 25.1 per cent). Twenty-eight per cent of the time lost by the total personnel was due to the respiratory diseases.

TABLE 4.—NUMBER OF CASES OF SICKNESS DISABILITY, NUMBER OF DAYS LOST AND AVERAGE DURATION PER CASE, CLASSIFIED BY CAUSES IN A GROUP OF 5074 WORKMEN DURING A PERIOD OF 7 YEARS.

Name of diseases.	Number of cases.			Number of days lost.			Average duration per case in days.		
	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.
Influenza (11) . . .	3963	1610	5573	38113	21069	59182	9.6	13.1	10.6
Tonsillitis and pharyngitis (109)	771	173	944	7209	1928	9137	9.3	11.1	9.7
Other respiratory diseases (97-107)	1432	500	1932	11447	5940	17387	8.0	11.9	9.0
Total respiratory diseases	6166	2283	8449	56769	28937	85706	9.2	12.7	10.1
Appendicitis (117) .	367	37	404	12657	1039	13696	34.5	28.1	33.9
Ulcer of stomach and duodenum (111 a-b) .	80	6	86	3935	488	4423	49.2	81.3	51.4
Other gastrointestinal diseases (112-116, 119-127) .	1734	783	2517	12238	5946	18184	7.1	7.6	7.2
Total gastrointestinal diseases	2181	826	3007	28830	7473	36303	13.2	9.0	12.1
Malaria (5)	1466	1678	3144	16862	21639	38501	11.5	12.9	12.2
Tuberculosis pulmonary (31)	46	20	66	11168	3548	14716	242.8	177.4	223.0
Contagious diseases (1-4, 6-10, 12-30)	296	121	417	4327	2135	6462	14.6	17.6	15.5
Veneral diseases (38-40)	217	285	502	5115	8097	13212	23.6	28.4	26.3
Infections (41) . . .	259	86	345	2848	1605	4453	11.0	18.7	12.9
Hernia (118 a) . . .	87	42	129	4046	2226	6272	46.5	53.0	48.6
Genitourinary diseases, nonspecific (130-142)	327	142	469	7034	4318	11352	21.5	30.4	24.2
Diseases of skin, boils, etc. (151-154)	554	224	778	5082	3057	8139	9.1	13.6	10.5
Home injuries (non-industrial) (165-203)	710	461	1171	11101	6518	17619	15.6	14.1	15.0
Rheumatism, neuralgia, arthritis, myositis, etc. (32, 82, 156, 158) . . .	806	535	1341	11764	7481	19245	14.6	13.9	14.4
Chronic heart and kidney diseases (87-91, 120) . . .	79	82	161	3596	6816	10412	45.5	83.1	64.7
All other diseases . . .	1601	881	2482	22469	11433	33902	14.0	13.0	13.7
Total	14795	7666	22461	191011	115283	306294	12.9	15.0	13.6

This difference in the races is noted in all classes of respiratory diseases, but is most marked in cases of tonsillitis and pharyngitis. These two diseases are not listed with the respiratory diseases in the International Classification, but are included with them in our study. The annual rates are, for whites, 33 per 1000 and for colored 15 per 1000, less than half in the latter group of the number in the former. The time lost per case is greater for the colored, but the time lost

per individual per year is .30 day for the whites and .16 for the colored, or slightly more than half as much by the colored as by the whites.

TABLE 5.—ANNUAL RATES OF SICKNESS DISABILITY, AVERAGE NUMBER OF DAYS LOST PER INDIVIDUAL PER YEAR, AND PERCENTAGE OF TIME LOST IN EACH DISEASE GROUP, IN A GROUP OF 5074 WORKMEN DURING A PERIOD OF 7 YEARS.

Name of diseases.	Annual rates per 1000.			Days lost per individual per year.			Per cent of total time lost.		
	White.	Col.	Total.	White.	Col.	Total.	White.	Col.	Total.
Influenza (11) . . .	167	136	157	1.61	1.79	1.64	20.0	18.3	19.3
Tonsillitis and pharyngitis (109)	33	15	27	.30	.16	.26	3.8	1.7	3.0
Other respiratory diseases (97-107)	60	43	54	.48	.50	.49	6.0	5.2	5.7
Total respiratory diseases	260	194	238	2.39	2.45	2.40	29.7	25.1	28.0
Appendicitis (117) .	16	3	11	.53	.09	.38	6.6	.9	4.5
Ulcer of stomach and duodenum (111 a-b) . . .	3	5	2	.17	.04	.13	2.1	.4	1.4
Other gastrointestinal diseases (112-116-119-127)	73	66	71	.52	.50	.51	6.4	5.2	5.9
Total gastrointestinal diseases . .	92	70	85	1.22	.63	1.02	15.1	6.5	11.9
Malaria (5)	62	142	89	.71	1.84	1.08	8.8	18.8	12.6
Tuberculosis pulmonary (31) . . .	2	2	2	.47	.30	.41	5.8	3.1	4.8
Contagious diseases (1-4, 6-10, 12-30)	12	10	12	.18	.18	.18	2.3	1.9	2.1
Veneral diseases (38-40)	9	24	14	.22	.69	.37	2.7	7.0	4.3
Infections (41) . . .	11	7	10	.12	.14	.12	1.5	1.4	1.5
Hernia (118 a) . . .	4	4	4	.17	.19	.18	2.1	1.9	2.0
Genitourinary diseases, nonspecific (130-142)	14	12	13	.30	.37	.32	3.7	3.7	3.7
Diseases of skin, boils, etc. (151-154)	23	19	22	.21	.26	.23	2.7	2.7	2.7
Home injuries (non-industrial) (165-203)	30	39	33	.47	.55	.50	5.8	5.7	5.8
Rheumatism, neuralgia, arthritis, myositis, etc. (52, 82, 156, 158) . . .	34	45	36	.50	.64	.54	6.2	6.5	6.3
Chronic heart and kidney diseases (87-91, 129) . .	3	7	5	.15	.58	.20	1.9	5.9	3.4
All other diseases . . .	67	75	70	.95	.97	.96	11.8	9.9	11.0
Total	623	651	632	8.05	9.79	8.62	100	100	100

In the group of gastrointestinal diseases the effect of race on morbidity is still further demonstrated. In this classification the annual rate for whites, 92, the duration per case 13.2, the days lost per individual per year, 1.22, and the percentage of time lost compared with the total time lost, 15.1 per cent, are all greater than for the colored which are: annual rate 70, duration 9 days, days lost per year .63, and percentage of total time lost 6.5. There were five

times as many cases of appendicitis per 1000 in white employees as in colored. Only a few of the 37 colored cases went to operation, and the accuracy of the diagnosis in other cases may be questioned, while nearly all of the 367 white men were operated upon. There were only 6 cases of gastric or duodenal ulcer in the colored group, and none of these were confirmed by radiographic examination. In the majority of the 80 white cases the diagnosis was sustained by radiography.

In the group of malaria cases, the picture is reversed. Here the colored employees predominate in frequency, which is more than double that of the whites, duration per case, days lost per individual per year ($2\frac{1}{2}$ times that of the whites), and percentage of time lost which is double that of the whites. Significant is the high percentage of time lost by the colored, 18.8 per cent of the total, bringing the percentage of time lost for the whole group up to 12.6 per cent from this preventable disease. The diagnoses in half of the cases of malaria were confirmed by microscope. The predominance of malaria in the colored group is probably due more to their increased exposure than to a racial susceptibility. As a rule the white employees live in screened houses, while the homes of most of the colored men are not screened.

Pulmonary tuberculosis shows identical rates for white and colored, but the whites show a longer duration per case and consequently a greater amount of time lost. The increased duration of the white cases was due to the fact that the mortality rate was much lower than that of the colored and they consequently had a much longer absence during convalescence. The relative frequency in our group does not correspond to that noted in the general population where the colored race shows a much higher frequency than the white.

Contagious diseases were slightly more prevalent in the white personnel than in the colored.

The picture presented in the gastrointestinal disease group is further exaggerated in the venereal diseases. The frequency in the colored men is almost three times that in the white and the days lost per individual more than three times that of the whites. These figures are not, of course, a true census of venereal diseases in the group, but represent only the cases discovered and losing time.

The whites showed a greater number of local infections, skin diseases and cases of furunculosis, than the colored.

The frequency of hernias is identical in both races, but the duration of disability is greater for the colored.

Home injuries are more frequent among the colored, but apparently less severe than among the whites. This conclusion is modified as in the tuberculosis cases by the fact that the mortality rate, which is not shown in this study, is higher for the colored than for the whites.

In the degenerative diseases of the heart and kidneys we again find a marked predominance in the colored race. The case rate is more than double and the disability rate more than three times those of the whites. Five and nine-tenths per cent of the time lost by the colored was from these diseases and only 1.9 per cent of the time lost by the whites.

The *conclusions* drawn from this study are that in this group of white and colored males:

1. The blood pressures of the colored are higher than those of the whites.

2. The pressures after 40 years of age advanced more rapidly in the colored race than in the white.

3. Damage to the aortic valve occurs earlier and more frequently in the colored than in the whites.

4. Albuminuria is more often functional in the white persons, and more often indicative of nephritis in the colored.

5. The frequency of illness is the same in both races.

6. The recuperative powers of the colored are less than those of the whites.

7. The whites are more susceptible to respiratory and other infections, to gastrointestinal diseases, especially appendicitis and gastric and duodenal ulcers, and to skin diseases, than the colored.

8. The colored men are more susceptible to rheumatic and degenerative diseases than the whites.

9. Venereal diseases and malaria are more prevalent among the colored probably because of greater exposure and less prophylaxis.

STUDIES IN ATHEROSCLEROSIS.

I. CONDITIONS IN CHILDHOOD WHICH PREDISPOSE TO THE EARLY DEVELOPMENT OF ARTERIOSCLEROSIS.*

BY PEARL ZEEK, M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, CINCINNATI, OHIO.

(From the Department of Pathology, University of Cincinnati and General Hospital.)

WHENEVER the complexities of a subject under investigation become so baffling that further progress seems impossible it is advisable to return to the simplest manifestations of the processes in question, and there seek out a new method of attack. That is what we have tried to do in relation to the centuries-old question of arteriosclerosis in studying its occurrence in young individuals.

* Read, in part, before the Annual Meeting of the Central States Pediatric Society, Cincinnati, Ohio, October 16, 1931.

From January 1, 1925, to January 1, 1931, there were 3072 autopsies performed on patients dying in the Cincinnati General Hospital. Of this number 1070 were under 30 years of age. These form the basis for this investigation. The material available for study consisted of the following: (1) Microscopic sections, averaging between 15 and 20 slides on each case, and including sections from all the principle viscera; (2) additional gross Zenker material and in many cases entire organs preserved in formalin or Kaiserling solution; (3) clinical and pathologic reports, the latter including both gross and microscopic findings.

The lesion dealt with in this investigation is the so-called simple arteriosclerosis, which begins as a degenerative process in the intima. In the early stages it is characterized by lipoid infiltration, in the later stages by fibrous tissue proliferation and calcification. There may also be ulceration and thrombosis, particularly when the process occurs in large vessels. When arterioles are affected they are likely to become occluded during the early stages of the process and the later changes may never occur. This report is not concerned with vascular changes of inflammatory origin as seen in syphilis, rheumatic fever and pyogenic infections. Periarteritis nodosa and thromboangiitis obliterans are also excluded.

A review of the pathologic material in these 1070 cases under 30 years of age revealed definite atherosclerosis of the aorta, arteries or arterioles in 79 cases. This figure does not represent the true incidence of atherosclerosis in this series. In many cases there was no formalin material available for fat stains. In such instances if the atheromatous change was so slight as to be questionable without special stains the case was not included.

The age distribution was found to be as in Table 1:

TABLE 1.—AGE DISTRIBUTION.

Age, years.	Total number studied.	Definite athero- sclerosis.		Chronic renal lesions.	Rheumatic heart disease.	Diabetes.	Tuber- culosis.
		No.	%				
Under 1	476	7	1.5	5			
1 to 5	154	2	1.3	2			
6 to 11	56	4	7.1	2	1	...	1
12 to 21	148	18	12.2	8	10	1	
22 to 29	236	48	16.1	27	12	3	4
	1070	79	7.4	44	23	4	5

It might be hoped that the 9 cases under 6 years of age would furnish very valuable data, in that they would present fewest complicating factors. However, all of these were found to be of unusual

complexity. Not one of them presented a simple diagnostic problem. A brief résumé of each case follows:

N-29-656, a stillborn, premature, breech-presentation, forceps delivery from a septic mother who died 13 days postpartum with acute pelvic peritonitis, bilateral salpingitis and septic lesions in other viscera. The baby had petechial hemorrhages in the viscera and, in addition, chronic foci of scarring and active inflammation in the kidneys. There was slight thickening of the renal arterioles and an area of definite atherosclerosis in the pulmonary truncus arteriosus. The latter lesion was so marked that there was actual narrowing of the lumen at that point. In addition, some of the pulmonary arterioles were thickened, apparently by intimal proliferation.

N-30-119, a stillborn, almost full-term delivery following premature separation of the placenta with bleeding. Delivery was followed by the passage of a large, fresh blood clot. The placenta was covered with much older clot. The fetal heart was definitely heard a few hours before delivery, but the child was born dead. There were a few definite atheromatous plaques in the pulmonary and coronary arteries, those in the former vessels being macroscopically visible. The lungs were edematous and atelectatic. There were a few petechial hemorrhages in the brain. The only other important findings were foci of lymphocytic infiltration and cellular degeneration in the kidneys and in the suprarenal medullæ.

N-30-416, an infant, aged 6 months, dying after a severe attack of diarrhea and bilateral otitis media in the late stages of which there was marked acidosis and urea retention. (Blood urea nitrogen, 105 mg.) The only pathologic changes in the kidneys were marked toxic swelling with extensive lipoid deposition in the tubules. Lipoids were also found in the thickened aortic intima and in the splenic arterioles. The splenic follicles were markedly hypoplastic and there was chronic inflammation in the pulp. The other findings were: Resolving lobular pneumonia, acute ulcerative esophagitis, subacute enterocolitis, early rickets and a terminal pulmonary embolus of undetermined origin.

N-29-356, a baby, aged 4 months, dying a few minutes after admission. No history was obtained. Autopsy findings: Chronic diffuse glomerulonephritis with marked renal arteriolar sclerosis; slight arteriolar sclerosis in the spleen, pancreas and liver; confluent lobular pneumonia; marked fatty infiltration in the liver; chronic periductile inflammation in the pancreas.

N-29-261, an infant, aged 10 months, developing convulsions in the terminal stage of bilateral otitis media. At autopsy petechial hemorrhages were found in the edematous brain and there were toxic changes in the viscera. The right kidney presented a moderate degree of hydronephrosis caused by what was apparently a congenital constriction in the right ureter. In this kidney there were wedge-shaped areas beneath the capsule which microscopically resembled very closely arteriolar nephrosclerosis. The vessels elsewhere in the kidneys and in the other viscera were not remarkable.

N-27-318, an infant, aged 9 months, dying with enteritis; no history was obtained. Autopsy findings: Chronic enteritis, generalized lymphoid hyperplasia, focal lymphocytic infiltration in suprarenal medulla, definite atheromatous thickening of aortic intima.

N-26-156, an infant, aged 3 months, dying with otitis media complicating whooping cough. There was subacute peribronchitis, follicular necrosis in the spleen, fatty infiltration in the liver and several definite atheromatous plaques in the aorta. The splenic arterioles had narrowed lumina apparently caused by endothelial proliferation over hyalin masses in their walls.

N-28-413, a very complicated case, aged 5 years, having numerous congenital abnormalities and many acquired defects. Child had received very poor care and had been sick since birth. The most important conditions found at autopsy were: Marked emaciation, hydrocephalus, bilateral cataracts, secondary anemia, jaundice, ascites, phimosis, pyelitis, all stages of focal nephritis, rickets, dental caries, abscesses in the scalp and gastroenteritis. There was arteriolar sclerosis in the kidneys, spleen, liver and thyroid. Unfortunately no section of aorta was saved.

N-28-237, an infant, aged 17 months, dying with lobular pneumonia complicating whooping cough. The white cell count before death reached 170,000, with 80 per cent lymphocytes. There was marked hypoplasia of the Malpighian corpuscles in the spleen and the central arterioles had thickened walls. There was subacute and chronic focal glomerulonephritis with early renal arteriolar sclerosis. Many of the renal tubules were loaded with lipoids. Other findings were: Rickets, nodular proliferation of glandular tissue in suprarenal medullæ, increase in colloid in the thyroid, fine diffuse fatty infiltration in the liver.

Although these 9 cases revealed a great variety of pathologic lesions, there were a few points of similarity: (1) Seven of the 9 presented lesions in the kidneys; the only one of these cases in which the blood urea nitrogen was recorded showed marked urea retention. (2) Eight of the 9 presented chronic lesions somewhere in the body, some of which were certainly present before birth. (3) The only other findings which occurred with greater frequency in these cases than in the large group without arteriosclerosis were hypoplasia of the splenic corpuscles and lesions in the suprarenal medullæ.

In the next age group, 6 to 11 years, inclusive, only 4 of the 56 cases studied presented definite atherosclerotic lesions.

N-28-286, a child, aged about 9 years, had extensive suppurative pyelonephritis with marked intimal sclerosis of the medium-sized renal arteries and arterioles. The other findings were: Marked fatty invasion of the parathyroids, chronic splenitis, subacute and chronic laryngitis, fibrosis of the thyroid and pulmonary edema.

N-29-577, a child, aged 7 years; was very complicated. The findings were as follows: Hypoplasia of the cerebral arteries with massive cerebral hemorrhage; sickle-cell anemia; generalized lymphoid hyperplasia; hyperplastic bone marrow; acute bronchitis; multiple adenomatous nodules in the suprarenals; extensive chronic focal nephritis; atherosclerosis in the larger splenic arteries and the aorta; arteriolar sclerosis in the spleen, kidney and appendix.

N-29-297, a child, aged 7 years, had advanced pulmonary tuberculosis with caseation, cavitation, emphysema and extensive fibrosis. The process had extended through some of the vessel walls and lipoids were found in the thickened intima. There was focal lymphocytic infiltration in the suprarenal medullæ. The kidneys were not remarkable except for toxic changes.

The fourth case in this age group was a child, aged 10 years, dying with rheumatic pancarditis in which there was moderate atherosclerosis of the pulmonary arteries. No section of aorta was saved.

Of the 18 cases with atherosclerosis dying between the ages of 12 and 21 years, inclusive, 10 had rheumatic heart disease. The

vessels affected in these cases were particularly the pulmonary and coronary arteries and the first portion of the aorta. In the cases without atherosclerosis dying within this age period there was only 1 case of rheumatic heart disease and this one died with lobar pneumonia within 2 months of the onset of the rheumatic disease.

The remaining 8 cases in this age group all had chronic renal lesions. Two died of far-advanced arteriolar nephrosclerosis accompanied by generalized small vessel sclerosis. Six others presented chronic renal lesions of less severe degree, death having been the result of other causes. One of these died in diabetic coma at the age of 17 years and presented large atheromatous plaques in the aorta. Splenic follicular hypoplasia and suprarenal lesions occurred in 2 cases each. No other lesion occurred with any notable degree of frequency.

The last age group to be considered consisted of 48 cases dying between the ages of 22 and 29 years, inclusive. Although these were not "pediatric" cases at the time of death, many of the lesions showed evidence of origin in childhood, and this fact was often verified by the clinical history.

Here again we find rheumatic heart disease and chronic renal disease occurring with striking frequency. Twelve (25 per cent) of the 48 atherosclerotic cases had rheumatic heart disease. Only 1 of the nonatherosclerotic cases had rheumatic heart disease. This was a woman, aged 28 years, who died following a septic abortion, with vegetative endocarditis superimposed upon a mitral stenosis, which was believed to be rheumatic in origin.

Chronic renal lesions occurred in 27 cases of this age group. In 11 of these it was the cause of death, 6 presenting diffuse glomerulonephritis and 5 advanced arteriolar nephrosclerosis. Sixteen others had chronic lesions in the kidneys, but died from other causes (7 from rheumatic heart disease). The only other pathologic change which occurred with any notable frequency in this group consisted of lesions in the suprarenal medullæ (in 19 cases). In 2 of these there were adenomatous nodules, in 1 focal necrosis and in 16 chronic focal inflammation in the medullæ. There was splenic follicular hypoplasia in only 4 of this age group. Syphilitic lesions were found in 5 cases; tuberculosis was the cause of death in 4.

Summing up the pathologic findings in these 79 cases, it is readily discernible that chronic renal lesions and rheumatic heart disease occur with entirely too great a frequency in this group to be coincidental. This is further borne out by the fact that in the rheumatic cases the atheromatous changes occurred almost exclusively in the larger pulmonary and coronary arteries and in the ascending aorta, while in the nephritic cases vascular lesions were most striking in the arterioles of the kidneys. In the rheumatic cases there were also atheromatous lesions in the mural and valvular endocardium which closely assimilated the intimal lesions in the arteries.

Only 4 cases of diabetes mellitus came to autopsy during these age periods. All of them had atheromatous lesions in the aorta. Joslin,² in 1929, referred to the frequency with which arteriosclerosis was found by the Roentgen ray in diabetic children.

The association of arteriosclerosis with renal lesions in children has been described by many investigators, the earliest writers on the subject being Gull and Sutton,¹ in 1872.

Pappenheimer, Von Glahn³ and others have described arterial lesions associated with rheumatic heart disease, but the changes which they describe are not the same as the atheromatous lesions dealt with in this study.

Whether or not the lesions encountered in the spleen and suprarenals have any direct relationship to arteriosclerosis has not been ascertained. They certainly occurred with a considerably greater frequency in the atherosclerotic cases than in the nonatherosclerotic cases of the younger age groups.

In 5 cases of far-advanced pulmonary tuberculosis with fibrosis and emphysema of the lungs atheromatous changes were found almost exclusively in the pulmonary vessels. However, there were many cases of tuberculosis in which no atheromatous changes were found.

In every one of the 79 cases presenting atherosclerosis chronic lesions were found in one or more of the viscera, irrespective of the age of the patient.

A discussion of arteriosclerosis in children would be incomplete without reference to the large amount of experimental work being done at present on the subject of hypervitaminosis. It has been conclusively demonstrated experimentally that marked vascular changes with calcification are produced by toxic doses of irradiated ergosterol. That the calcification in the vessels is preceded by lipid deposition and is identical with the process of atherosclerosis in human beings, has not been so unquestionably proven, although certain investigators claim to have demonstrated the similarity of these lesions by giving less toxic doses, thereby slowing up the process so that the early precalcification stages could be observed. Shelling⁴ believes that the toxicity of viosterol depends upon the following factors: (1) Differences in the potency of the irradiated product; (2) age of the recipient; (3) length of time of administration; (4) character of the diet in regard to its content of calcium and phosphorus. It is not known at present whether administration of any of the irradiated products on the market has ever produced vascular lesions in children. It is commonly believed by practitioners and firmly assured by drug houses that therapeutic doses are not harmful. However, caution demands: (1) That administration be kept within the hands of a physician; (2) that in the determination of dosage such factors as diet, age of the patient and degree of need for the irradiated product be carefully considered.

Conclusions. 1. A review of 1070 consecutive autopsies on individuals under 30 years of age revealed atherosclerosis occurring with far greater frequency in connection with certain disease conditions than with others.

2. Rheumatic heart disease was almost invariably accompanied by atheromatous changes in the aorta, pulmonary or coronary arteries.

3. All of the 4 diabetic cases presented atherosclerosis of the aorta.

4. Chronic renal lesions were found in 34 of the 52 nondiabetic nonrheumatic cases which presented atherosclerosis, and were present also in 10 of the 23 rheumatic cases. The renal arterioles were the vessels most frequently involved in these cases.

5. The only other pathologic lesions which occurred with notable frequency in the atherosclerotic group were: (1) Focal lesions in the suprarenal medullæ and (2) hypoplasia of the Malpighian corpuscles in the spleen.

REFERENCES.

1. Gull, Sir Wm. W., and Sutton, H. G.: Chronic Bright's Disease, *Med. Chir. Trans.*, 1872, 55, 273.
2. Joslin, E. P., and White, P.: Diabetic Children, *J. Am. Med. Assn.*, 1929, 92, 143.
3. Pappenheimer, A. M., and Von Glahn, W. C.: Studies in the Pathology of Rheumatic Fever, *Am. J. Path.*, 1927, 3, 588.
4. Shelling, D. H.: Relation of Calcium and Phosphorus of the Diet to Toxicity of Viosterol, *Proc. Soc. Exp. Biol. and Med.*, 1930, 28, 298.

STUDIES IN ATHEROSCLEROSIS.

II. ATHEROMA AND ITS SEQUELÆ IN RHEUMATIC HEART DISEASE.

BY PEARL ZEEK, M.D.,
ASSISTANT PROFESSOR OF PATHOLOGY,
CINCINNATI, OHIO.

(From the Department of Pathology, University of Cincinnati and General Hospital.)

IN the previous paper the strikingly regular association of some degree of atheroma with rheumatic heart disease was brought out. With the hope that an investigation of this association might shed some light on the subject of atherosclerosis, the clinic and pathologic material on all cases of rheumatic fever which came to autopsy during the last 6½ years has been collected and analyzed.

For this report only cases of undoubted rheumatic origin have been included. These numbered 62 (of 3372 autopsies), in each of which either typical active rheumatic lesions were found at autopsy,

or, in the inactive cases, a typical rheumatic history was obtained. The criterion for the former was the presence of verrucous endocarditis, not showing bacteria by the ordinary methods, accompanied by Aschoff nodules in the myocardium and usually associated with a pericarditis. A "typical rheumatic history" included signs and symptoms of cardiac disease accompanying or promptly following an attack of acute polyarthritis. The cases ranged in age from 7 to 66 years, but most of them were under 40 years of age at death. There were 36 males and 26 females, 39 white and 23 colored. Twenty-one cases died as a direct result of the cardiac lesions without any complication other than severe decompensation. The immediate causes of death in the other 41 cases are found in Table 1:

TABLE 1.—CAUSES OF DEATH.

	Number of cases.
Superimposed acute vegetative endocarditis	13
Lobular pneumonia	6
Lobar pneumonia	4
Pulmonary embolus (right atrial thrombosis)	4
Extensive mural thrombosis (left ventricular thrombi, 2; left atrial thrombi, 1)	3
Cerebral embolus	2
Collapse of left lung	2
Coronary occlusion	1
Diffuse glomerulonephritis with uremia	1
Septic abortion	2
Ruptured appendix	1
Cirrhosis of liver (with ruptured esophageal varices)	1
Subarachnoid hemorrhage of undetermined origin	1
Total	41

Methods. In each of the 62 cases there were available for study a pathologic report, microscopic sections stained with hematoxylin and eosin, the original paraffin blocks and extra Zenker material kept in dilute alcohol. In a considerable number of cases the entire heart and occasionally portions of other organs had been preserved in formalin or Kaiserling solution and were available for study. The fat stains used on the latter were (a) Herzheimer's Scharlach R,¹ made up with caustic soda, and (b) osmic acid, both before and after treating the sections with potassium dichromate. It was found that by slightly modifying the usual osmic acid technique the potted Zenker material permitted a demonstration of lipoids almost as constantly and clearly as the osmic acid-potassium dichromate technique on formalin material. Evidently the dichromate in the Zenker solution fixes the lipoids in such a way that they are not entirely dissolved by alcohol of 60 to 80 per cent concentration even after 6 years.

Generalized arteriosclerosis worthy of note was found in only 15 cases and 12 of these were past 40 years of age. One of the other 3 was 35 years of age and had hypertension. The other 2 were 17 and 33 years of age, respectively.

The incidence of atheroma in the aorta, coronary arteries and pulmonary arteries in these 62 cases of rheumatic heart disease is found in Table 2.

TABLE 2.—INCIDENCE OF ATHEROMA IN RHEUMATIC HEART DISEASE.

Degree of atheroma.	Aorta.	Coronary arteries.	Pulmonary arteries.
Marked	16	12	9
Moderate	31	18	18
Slight	9	14	20
None	2	13	12
No section	4	5	3

The criteria employed for the various degrees of atheroma were as follows:
 "Marked"—large, well-formed or numerous atheromatous plaques, or atheroma with calcification.

"Moderate"—numerous atheromatous patches, or small plaques not calcified.

"Slight"—definite atheromatous infiltration but no well-formed plaques or calcification.

"None"—no evidence of atheroma in the intima (in most of the cases in this category only 1 or 2 nonselected sections were available).

The incidence of atheroma in the various age groups is found in Table 3:

TABLE 3.—INCIDENCE OF ATHEROMA BY AGE GROUPS.

Age.	Total number of cases.	Marked atheroma.			Moderate atheroma.			Slight atheroma.			No atheroma.			No sections.		
		Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.	Aorta.	Coronary.	Pulmonary.
10 yrs. or less	2	0	0	0	1	0	1	0	1	1	0	1	0	1	0	0
11 to 20 . .	10	2	2	1	1	3	2	5	3	2	1	4	2	1	1	1
21 to 30 . .	16	2	1	1	13	3	3	1	3	9	0	7	3	0	1	0
31 to 40 . .	11	0	1	0	6	3	4	3	5	3	1	1	3	1	2	2
41 to 50 . .	11	5	1	3	5	5	5	0	1	3	1	1	3	0	0	0
51 to 60 . .	10	5	5	3	3	5	3	0	0	3	2	0	0	0	0	0
61 to 70 . .	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Totals	62	16	12	9	31	18	18	9	14	20	2	13	12	4	5	3

It is to be noted that of 28 cases of rheumatic heart disease in which death from any cause occurred before 31 years of age 25 presented some degree of atheroma in the aorta. In 19 of these there were well-defined plaques (atheroma in the deep intima with superimposed fibrous tissue proliferation). In 4 cases the plaques were large or numerous and some contained calcium. Two of these 4 cases were under 20 years of age. Seventeen of 28 cases also had demonstrable atheroma in the coronary arteries, marked in 3 cases and of moderate degree in 6. The pulmonary arteries were atheromatous in 20 of the 28 cases, markedly so in 2 of them and only moderately in 6.

The question which is raised by these observations is whether or not there is any relation, other than coincidence, between the

rheumatic heart disease and the early development of atherosclerosis. That atheroma occurs in the young unassociated with rheumatic heart disease has been established by many investigators.² This group of cases, however, presents a higher incidence of atheromatous changes in the locations noted than has been reported hitherto for the same age group with death from any cause.

There are passing references in the literature to the occurrence of lipid deposits both inside and outside of vessel walls in rheumatic fever. In his review of the pathology of rheumatic fever, in 1926, Sachs³ quotes Baehr: "The lime and cholesterin deposits often seen in such vascular lesions are evidence of an atherosclerotic process which has occurred here much more rapidly and far more extensively than elsewhere in the vascular system because of the unusual degree of mechanical strain to which such an abnormal valve is subjected. The destruction of elastica or disarrangement of elastic fibrils as a result of the original inflammatory process evidently results in increased replacement fibrosis and atheroma, as it would elsewhere in the cardiovascular apparatus." Sachs remarks: "Further studies are required to elucidate the precise rôle of chronic inflammation and the factor of strain in the production of rheumatic chronic valvular disease." Pappenheimer and Von Glahn⁴ mention atheromatous changes only to assure the reader that the lesions they are describing are not those of atherosclerosis.

It should be emphasized that the pathologic changes discussed here are not the lesions of rheumatic fever in the vessel walls described by Klotz, Pappenheimer, Von Glahn and others. This present report, in no instance, includes under the term "atherosclerosis" those lesions definitely inflammatory in nature so characteristic of rheumatic disease in the vascular tree. Such lesions were found in the great majority of the above 62 cases. The atheromatous changes have not seemed to be particularly related to them, although they frequently occur together in the larger vessels. In the arterioles, however, particularly those at the base of rheumatic valves, which so frequently present proliferative endarteritis, no lipoids have been found.

Von Glahn,⁵ Stewart and Branch (cited by Von Glahn) and others have mentioned the occasional deposition of calcium salts in rheumatic lesions. Winkelstein (cited by Sachs) reported calcification and ossification of the pericardium in a case of purulent pericarditis complicating rheumatic heart disease. Since calcification of bloodvessels is usually preceded by atheroma it was considered worth while to investigate the endocardial lesions with special reference to lipid changes.

In no case was calcification of the endocardium encountered without demonstrable lipid changes in surrounding areas. In fact, the calcium salts often appeared to be plastered on top of masses of lipoids (Fig. 5). Lipoids, however, were often found without

TABLE 4.—CORRELATION OF CARDIAC LESION WITH DEGREE OF ATHEROMA.

Case No. age at death.	First known attack of polyarthritis; time before death.	Onset of cardiac symp- toms; time before death.	Cardiac lesions.					Degree of atheroma.			
			Myocardium.	Mitral.	Aortic.	Tricuspid.	Pulmonary.	Pericardium.	Aorta.	Coronary arteries.	Pulmonary arteries.
N-25-107 10 yrs.	8 mos.	3 yrs.	Scarred; activity	Scarred	Scarred	n	n	Oblit. fibrous and fibrinous adhesions	Unknown	None	Moderate;
N-25-182 22 yrs.	2 yrs.	2 yrs.	Many scars; activity	Scarred	Scarred	n	n	Oblit. fibrous adhesions	Marked	Slight	Moderate.
N-25-269 21 yrs.	None	4 yrs.	Markedly scarred; activity	Scarred; fun- gating veg.	Scarred	n	n	Oblit. fibrous and fibrinous adhesions	Slight	None	Slight.
N-29-60 29 yrs.	None	"In child- hood"	Scarred; activity	Stenosis	Stenosis	n	n	Hydropericard.; beginning fib- rinous exudate	Moderate	Marked	Slight.
N-29-159 27 yrs.	4 wks.	Unknown	Sl. scarred; activity	Scarred; activity	Sl. scarred; activity	n	n	Oblit. fibrino- pur. exudate	Moderate	None	None.
N-26-183 18 yrs.	8 yrs.	1 mo.	Marked activity	Stenosis	Activity	n	n	Chr. focal epi- carditis; hy- dropericard.	Slight	Slight	None.
N-26-210 20 yrs.	1 yr.	5 yrs.	Scarred; activity	Stenosis; Str. viridans veg.	Sl. scarred	n	n	No adhesions	Slight	Moderate	Slight.
N-26-229 29 yrs.	8 yrs.	8 yrs.	Scarred; activity	Scarred; sl. stenosis	Sl. scarred	n	n	Oblit. fibrous adhesions	Moderate	Unknown	Moderate.
N-26-332 16 yrs.	3 yrs.	3 yrs.	Scarred	Stenosis	Stenosis	Sl. scarred	n	Oblit. fibrous adhesions	Marked	Moderate	Moderate.
N-26-387 11 yrs.	5 yrs.	Unknown	Activity	Scarred; activity	Scarred; activity	Scarred; activity	n	Chr. focal epi- carditis; few adhesions	Slight	Marked	None.
N-27-158 16 yrs.	2 yrs.	3 wks.	Activity	Activity	Activity	Activity	n	Oblit. subacute inflam.	Slight	None	None.
N-27-220 18 yrs.	2 mos.	3 wks.	Activity	Activity	n	n	n	n	Unknown	Slight	None.
N-28-115 24 yrs.	2 mos.	Recent	Activity	Activity	n	n	n	n	Moderate	Moderate	None.
N-28-169 25 yrs.	1 yr.	1 yr.	Activity; mural thrombi	Stenosis; activity	Activity	Activity	n	Mark. scarred; no adhesions	Moderate	None	Marked.

N-28-340 23 yrs.	Unknown	Unknown	Abscesses; thrombosis	Stenosis; activity	Sl. scarred	n	n	Unknown	Moderate	None	Slight.
N-29-278 29 yrs.	Unknown	"Years ago"	Markedly scarred	Stenosis; calcification	n	n	n	No adhesions	Moderate	Slight	Slight.
N-29-330 22 yrs.	"Repeated attacks for years"	"Early childhood"	Mural thrombi	Scarred; activity	n	Scarred; activity	n	No adhesions	Moderate	Moderate	Moderate.
N-29-457 13 yrs.	6 wks.	5 wks.	Activity	Sl. scarred; activity	Activity	n	n	Oblit. organizing fibrinous exudate	Slight	Unknown	None.
N-29-541 17 yrs.	7 mos.	Unknown	Sl. scarred; activity	Activity	Activity	Activity	Activity	No adhesions	Marked	Slight	Slight.
N-30-246 27 yrs.	8 yrs.	Several years	Markedly scarred; activity	Stenosis; fungating veg.	Scarred; fungating veg.	Scarred; rheumatic activity	n	Fibrous and fibrinous adhesions	Moderate	None	Slight.
N-30-407 26 yrs.	"Repeated attacks for many years"	Over 4 yrs.	Scarred	Sl. scarred; fungating veg.	Sl. scarred; fungating veg.	n	n	n	Moderate	Moderate	Slight.
N-30-576 17 yrs.	"Growing pains"	12 yrs.	Markedly scarred	Stenosis	Stenosis; calcification	n	n	No adhesions; chr. epicard.	Unknown	Marked confluent plaques	Moderate.
N-31-69 17 yrs.	None	2 yrs.	Diffusely scarred	Stenosis; calcification	Stenosis; calcification	Scarred; early stenosis	n	Hydropericard.	Moderate	Moderate	Marked.
N-31-71 26 yrs.	Unknown	Unknown	Activity	Activity; also bac. endocardium	n	n	n	n	Moderate	None	Slight.
N-31-118 25 yrs.	Unknown	Unknown	Markedly scarred; activity	Scarred	Scarred	n	n	Oblit. fibrinous adhesions	Moderate	Slight	Slight.
N-31-194 24 yrs.	18 yrs.	Markedly scarred	Markedly scarred	Stenosis; calcification	Scarred	Stenosis; calcification	Scarred	Oblit. fibrinous adhesions	Marked	Slight	Slight.
N-31-300 7 yrs.	3 mos.	1 wk. (?)	Activity	Activity	n	n	n	Oblit. fibrinopur. exudate	Moderate	Slight	Slight.
N-25-260 30 yrs.	13 yrs.	15 yrs.	Activity	Stenosis	Sl. scarred	n	n	Hemopericardium	Moderate	None.	None.

calcium salts being present. Frequently the lipid droplets occurred in parallel rows, apparently following the course of degenerating elastic fibers. This appearance has been noticed frequently in atheromatous aortas. At other times the droplets occurred inside endothelial cells, particularly those covering the ventricular surface of the mitral valve (Fig. 3). Lipoid changes were observed not only in the valvular endocardium but also in the lining of the left atrium, most frequently in the elastic layer of areas involved in rheumatic endocarditis.

These lipoids stained readily with Scharlach R and with osmic acid. They were found to be doubly refractile under the polarizing microscope. Occasionally cholesterol crystals were present in the lipid masses. These remained unstained by the Zenker-osmic acid technique (Fig. 4). By none of the methods employed could any difference be detected between the atheromatous changes occurring in the endocardium of young individuals suffering from rheumatic heart disease, and those changes in the aorta which are commonly found in much older individuals.

In Table 4 the degree of atheroma is checked against the extent and duration of cardiac involvement and the age of the patient.

Just as there is no constant relationship between the extent of the cardiac lesions and the duration of the rheumatic disease, so the degree of atheroma cannot be predicted from these facts. Undoubtedly that elusive quality called individual susceptibility plays a large rôle in the development of atheroma in rheumatic disease. A familial, if not actually an hereditary factor, has long been suspected in both rheumatic disease and atherosclerosis. Nevertheless, the degree of atheroma in many of these cases can be seen to correspond more or less to the severity of the disease as judged by the other data given in the table.

At just which stage of the disease the atheromatous changes begin is uncertain. In Case N-31-300, aged 7 years, and having a reliable history of rheumatic disease of not more than 3 months' duration with cardiac involvement for a much briefer period, there were a few yellow plaques in the ascending aorta large enough to be easily visible to the naked eye. There was no valvular stenosis, yet lipoids were readily demonstrable microscopically in the pulmonary arteries. Case N-31-71, a much older patient, but with lesions very similar to those of the preceding case, presented about the same degree of atheroma in the aorta and pulmonary arteries.

Negative or inconsiderable findings of atheroma in the preceding tables possess relatively little significance because the only sections available in many of these cases were taken merely as a matter of routine, without particular regard for atheromatous plaques, and these were stored later in alcohol. That atheroma in rheumatic disease is even more frequent and more marked than indicated in the above tables has been proven by autopsies performed since the beginning of this investigation.



FIG. 1.—Large pulmonary artery with intima loaded with lipoids. Case N-31-69, aged 17 years. Scharlach R—hematoxylin.

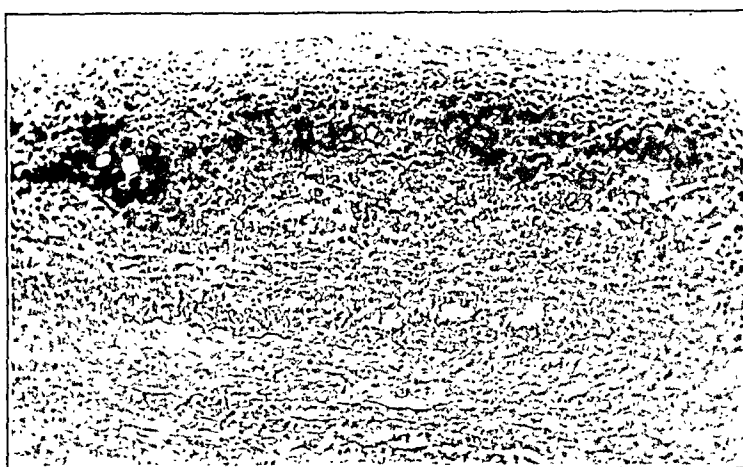


FIG. 2.—Aorta with intima loaded with lipoids. Note elastica interna. Case N-26-332, aged 16 years. Zenker-osmic Giemsa.



FIG. 3.—Mitral valve with very early lipid infiltration. Note lipoids inside endothelial cells. Case N-31-71, aged 26 years. Zenker-osmic Giemsa.

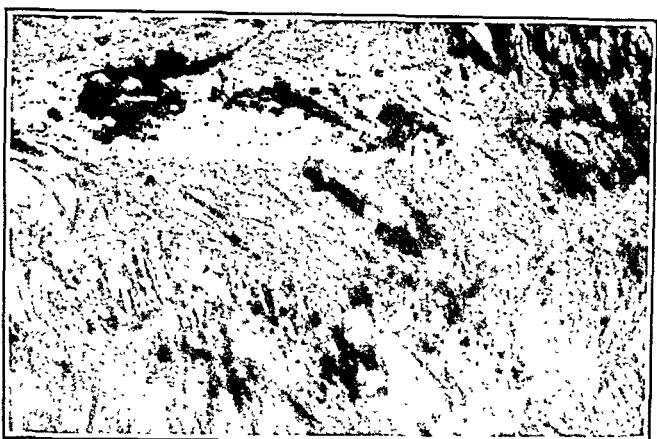


FIG. 4.—Mitral valve with lipoid infiltration. Note unstained cholesterol crystals. Case N-26-159, age 27 yr. Zenker-osmic-Van Gieson.



FIG. 5.—Mitral valve with lipoid infiltration and extensive calcification. Case N-31-69, aged 17 years. Scharlach R—no counterstain used.

Because of the difficulties in obtaining reliable "negative" material, control cases are presented here with some reservation. It may be stated with assurance, however, that in the hundreds of cases under 30 years of age which have been examined microscopically for atheroma, and material from which has been preserved in a similar manner, the incidence of atheroma, in the group as a whole, is decidedly lower than that in the rheumatic cases.

There are 2 cases, however, which will be cited because of their particular value as controls.

Case Abstracts. N-29-399, a white girl, aged 11 years, suffered a severe abrasion over the right eye. Subsequently she developed hemolytic streptococcus septicemia and died 6 weeks after the accident. The autopsy findings were multiple abscesses in the viscera with streptococcus vegetations on the mitral and tricuspid valves, with septic pulmonary infarcts. No evidence of atheroma, either gross or microscopic, was found anywhere. A reliable history and a complete autopsy presented no evidence of rheumatic disease.

N-31-87, a negro, aged 30 years, was admitted to the hospital complaining of painful, swollen joints of 2 weeks' duration. He had never had a previous attack, but had suffered from tonsillitis for years. Physical examination was essentially negative except for the signs of acute polyarthritis involving both ankles, the right wrist and right shoulder. Shortly after admission the patient developed lobar pneumonia and died. At no time were there any signs or symptoms of rheumatic heart disease. The autopsy findings were essentially negative except for lobar pneumonia and acute polyarthritis. No rheumatic lesions were found in the heart and there was no evidence of atheroma either gross or microscopic.

Is atheroma in rheumatic disease a transient phenomenon or is it progressive? Whether or not the lipoids are ever reabsorbed has never been determined. However, one fact established beyond any doubt is that there is a decided tendency for atheromatous areas to become calcified. Case N-31-69 was under observation and treatment for over 2 years. The course of the rheumatic disease was carefully studied as it progressed from valve to valve. At autopsy the location of the calcified areas on both the mitral and aortic valves was demonstrably in atheromatous lesions (Fig. 5). It was this case which furnished the first convincing link between the suspicion and the proof that calcified stenotic valves found in adults are rheumatic in origin. This subject will be discussed more fully in a subsequent report.

Are the lipid deposits in rheumatic heart disease limited to valvular endocardium and the intima of the aorta, coronary and pulmonary arteries? In these 28 cases under 31 years of age no other vessels were affected with any regularity. In a considerable number of patients dying during an active rheumatic attack, an acute or subacute polyserositis was found, and in some of these there were remarkable lipid deposits beneath the exudate, in the splenic capsule, in the pleura and, in 1 case, within and beneath the mesothelial cells of the uterine peritoneum. In some of these

same cases there were considerable lipid deposits in the tubular epithelium of Henle's loops in the kidney.

Many other questions have been raised by these observations which cannot be answered at the present time. Why do atheromatous changes occur particularly in mesodermic tissues? What does rheumatic disease have in common with the relatively few other conditions which are found to predispose to the early development of atherosclerosis?

Summary. 1. Sixty-two cases of rheumatic heart disease have been analyzed with reference to the incidence of atheroma, particularly in the aorta, coronary and pulmonary arteries.

2. In 28 cases under 31 years of age the degree of atheroma has been compared with the duration and extent of the cardiac lesions.

3. Rheumatic heart disease has been found to predispose to the early development of atheromatous lesions in the aorta, pulmonary and coronary arteries, and also in the valvular and left atrial endocardium. Lipoid deposits also have been found, in some cases, in the inflamed serous membranes and in certain renal tubules.

4. Lipoid deposition has seemed to begin soon after the onset of cardiac disease, and, in a very general way, has paralleled in degree the cardiac lesions.

5. The atheromatous changes, in many cases, have been progressive, leading to calcification and, when in the valvular endocardium, accentuated stenosis.

BIBLIOGRAPHY.

1. Herzheimer, G.: Deutsch. med. Wchnschr., 1901, 27, 607.
2. Zeek, P.: Juvenile Arteriosclerosis, Arch. Path., 1930, 10, 417.
3. Sachs, B.: The Pathology of Rheumatic Fever: A Critical Review, Am. Heart J., 1926, 1, 750.
4. Pappenheimer, A. M., and Von Glahn, W. C.: Studies in the Pathology of Rheumatic Fever, Am. J. Path., 1927, 3, 588.
5. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, Am. J. Path., 1926, 2, 1.

THE PROGNOSTIC VALUE OF REPEATED BLOOD CULTURES IN PNEUMOCOCCUS LOBAR PNEUMONIA.

By K. R. KOCH, M.D.,

BACTERIOLOGIST TO WESTERN PENNSYLVANIA HOSPITAL, PITTSBURGH, PA.

(From the Institute of Pathology, The Western Pennsylvania Hospital.)

In acute infectious diseases such as pneumococcus lobar pneumonia the demonstration of a bacteremia by blood culture is of clinical value only under two conditions: (1) The information gained should be of benefit to the patient and the physician; (2) the culture method should not be complicated and yield results within 18 hours or less. While knowledge concerning the prognosis is not necessarily valuable *per se*, it becomes a matter of definite

practical interest, when the efficiency of a mode of treatment is to be evaluated.

Reports on the incidence of bacteremia in lobar pneumonia vary. Rosenow reported the presence of bacteria in the blood stream in 91 per cent of a series of patients, while other authors cultivated pneumococci in but 20 to 30 per cent of their patients.

The presence of a few bacteria in blood samples taken at frequent intervals and cultivated by refined methods should certainly be distinguished from a bacteremia readily shown in 1 or 2 cc. of blood. Some years ago it was pointed out by Sutton and Sevier,¹ and later again by Rosenblueth,² that for comparison purposes the separation of patients by blood culture into positive and negative groups is too arbitrary and ignores the degree of bacterial invasion, which is really the more important factor.

In the present investigation an attempt has been made to determine by a simple technique requiring small amounts of blood the degree of pneumococcus blood stream invasion and its changes in patients admitted to the hospital.

Method. The blood culture method consisted of inoculating 2 cc. of whole blood into 50 cc. glucose glycerophosphate broth at the bedside of the patient. At the same time an agar plate was poured with 1 cc. of patient's blood. Blood was always obtained from the same arm vein.

The glycerophosphate medium is prepared as follows: To veal-heart infusion add 1 per cent Difco peptone, 0.5 per cent NaCl and 1 per cent sodium glycerophosphate (anhydrous, powdered, Mallinckrodt). Boil for 1 hour, filter, autoclave for 20 minutes at 15 pounds' pressure and add 1 per cent glucose in sterile solution. The addition of glycerophosphate serves three purposes: The reaction of the medium is automatically brought to pH 6.8 to 6.9, no titration being necessary; the substance acts as a buffer and enriches the medium by its content of glycerin. Disodium glycerophosphate as a buffer was introduced by Mellon, Acree, *et al.*³ in 1921, and has proved its value as indicated during the interval. Moreover, this broth is more resistant to hydrogen-ion change when autoclaved at pH 8 than are media buffered with other phosphates. In addition, calcium and magnesium salts of glycerophosphate are soluble.

Pneumococci present in the blood stream to such a degree that one or more organisms appear on the blood plate inoculated with 1 cc. of patient's blood grow with a definite and characteristic change of the broth during 16 hours' incubation at 37° C. The medium becomes turbid throughout and has a dark greenish-brown color. If the degree of bacteremia is small, and no colonies are seen on the plate, the characteristic changes of the medium appear after 24 to 72 hours' incubation. Experience has shown us that the blood culture can be considered sterile if no growth appears after 72 hours' incubation.

The upper layer of a positive culture (or a centrifuged specimen, if the culture was shaken up) is used for the determination of the pneumococcus type. Distinct and specific precipitation takes place with type precipitin serum in a water bath at 56° C. within 1 to 10 minutes or often even at room temperature without incubation, if the tubes containing the culture-serum mixture are shaken for a few minutes. It happened in several instances that the blood culture precipitated Types I or II serum, while repeated sputum examinations from the same patient yielded only Type IV pneumococcus. But it was never observed that the blood culture was

Type IV when we recovered Types I or II from the sputum of the same patient. Diagnostic sera vary in their flocculation ability to a considerable degree; a very satisfactory serum was prepared in rabbits by the method described by Cole and Moore.⁴

FC AGE 27 PNEUMOCOCCUS TYPE 4

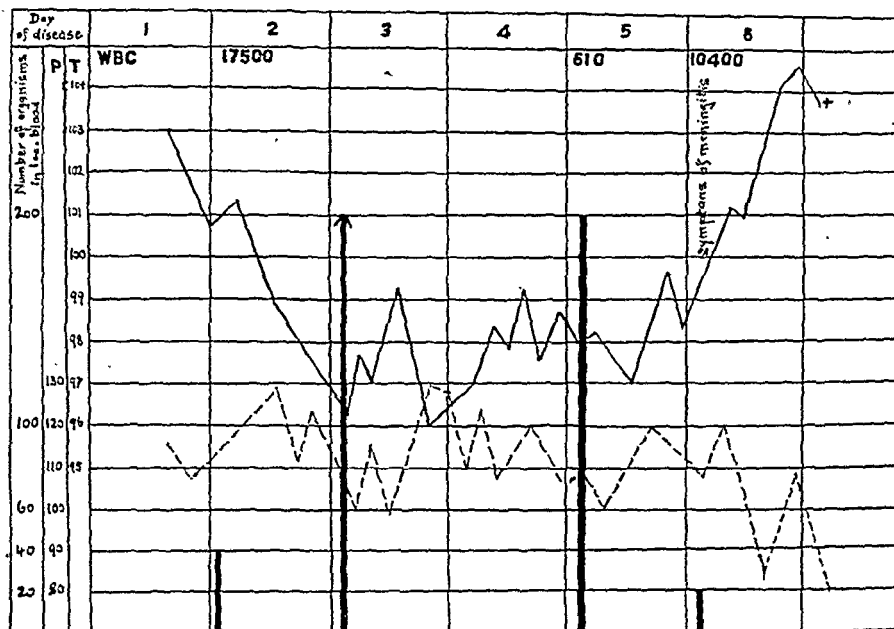


CHART I.—F. C., a white man, admitted to the hospital with pneumococcus Type IV lobar pneumonia. Columns indicate degree of bacteremia. The patient developed symptoms of meningitis on the 6th day and died 24 hours later of pneumococcus meningitis.

Results. This report is based upon the examination of blood cultures taken from 139 pneumococcus pneumonia patients during the first five months of 1931. Symptomatic treatment varied and followed the generally recognized procedures of therapy, although none of the patients was treated with antipneumococcus serum. From 45 patients a positive blood culture was obtained in one or more instances. A percentage of 32.4 per cent positive blood cultures compares favorably with the results obtained by other authors (Rosenblueth, 22.4 per cent; Schottmueller, 23 per cent; Cole, 27 per cent; Cecil, 29.7 per cent; MacLachlan, Kastlin, Lynch, 29.7 per cent. It seems justifiable to conclude that the technique used in this investigation is not less efficient than other methods, although the culture medium used is slightly acid. The mortality rate in our patients with positive blood cultures was 75 per cent. Cecil reported 78 per cent; Cole, 67 per cent; Rosenblueth, 85 per cent; MacLachlan, Kastlin and Lynch, 73 per cent. The distribution of types was as follows: Positive blood cultures: Type I, 18;

Type II, 22; Type IV, 5. In patients with negative blood cultures sputum examinations yielded Type II as often as Type I. Although Type III was not observed during the season, the incidence of positive blood cultures and the mortality rate in such patients correspond well with data furnished by several authors. The series under observation can, therefore, be considered as representing average cases.

Whenever a patient was admitted to the hospital with the diagnosis of pneumonia a blood culture was obtained by the method mentioned above. The degree of bacteremia, when present, was determined by counting the number of bacteria on the agar plate inoculated with 1 cc. of patient's blood. From the patients showing a bacteremia at admission daily blood cultures were obtained until the change in the degree of bacteremia was clearly indicated or the blood stream became sterile. From the series of 45 patients with a positive blood culture 14 were eliminated from consideration, because only 1 blood culture was obtained. Most of them died, before a second blood culture could be secured.

It was found that 20 patients showed an increasing or stationary number of pneumococci in the blood stream. None of the patients survived; the mortality in these patients was 100 per cent irrespective of the stage of the disease, the time of admission to the hospital or the degree of bacteremia, when the first blood culture was taken.

The increasing degree of bacteremia predicted a fatal outcome, from 1 to 10 days preceding death. That the increasing number of bacteria in the blood stream can be a more definite indicator of the prognosis than the general reaction of the patient is illustrated in the chart of the patient F. C. The patient died on the fourth day after the increase of bacteremia had been demonstrated.

TABLE 1.—PATIENTS WITH AN INCREASING OR STATIONARY DEGREE OF BACTERIA.

Type.	Name.	Age.	Onset.	Day of disease.										
				2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	14.
I.	F. C.	?	Acute	40	200	...	200	20	D					
	T. O.	40	3 with cold	60	180	D					
	C. E.	28	3 with cold	1	30	300	D							
	M. B.	55	Acute	2	30	200	D			
	A. K.	45	Acute	1	120			...	D	
	O. M.	27	Acute	40	200	...	Neg.	...		D				
	W. K.	32	Acute	100	...			35	100	...	D
	R. C.	50	Acute	1	D	...	D					
	J. N.	37	Acute	30	...	30	D	...						
	L. B.	?	?	40	150	D					
II.	M. W.	25	Acute		1	100		D	
	S. J.	?	?	20	...	200	D				
	J. W.	30	2 with cold	1	200	D			
	T. G.	46	1 with cold	1	30	200						D
	J. C.	55	Acute	1	30	30	30	125	125	D	
	W. S.	28	Acute	1	20	200	D					
	B.	?	?	200	200	D					
	E. F.	34	Acute	...	3	3	40	D						
IV.	P. S.	?	?	5	100	...	D				
	E. L.	35	Acute	40	200	D			

Figures designate number of pneumococci per 1 cc. of blood.

D = Death.

In 11 patients the degree of bacteremia decreased from day to day; 2 patients died (mortality, 17 per cent).

TABLE 2.—PATIENTS WITH A DECREASING BACTEREMIA.

Type.	Name.	Age.	Onset.	Day of disease.									
				1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
I.	E. P.	32	Acute	20	Neg.	D	
II.	C. E.	?	Acute	10	10	Neg.	...	Reco	vered		
	T. E.	30	Acute	..	20	10	1	Neg.	...	Reco	vered		
	W. S.	30	Acute	30	10	..	1	1	Neg.	..	Recovered
	E. L.	38	Acute	..	30	20	1	..	1	Neg.	Neg.	..	Recovered
	J. M.	?	Acute	1	Neg.	..	Reco	vered			
	M. V.	50	Acute	5	Neg.	..	Reco	vered					
	E. J.	?	Acute	..	1	1	Neg.	..	Reco	vered			
	J. H.	40	Acute	..	2	1	D						
	M. W.	35	Acute	1	4	Neg.	Neg.	..	Reco	vered			
	J. K.	16	Acute	..	1	Neg.	..	Reco	vered				
IV.	W. K.	38	Acute	..	1	Neg.	..	Reco	vered				

Figures designate number of pneumococci per 1 cc. of blood.

D=Death.

In 1 patient, A. S., aged 60 years, we observed a decrease from 50 organisms in 1 cc. of blood to 25 in the second blood culture and no growth in a third blood culture; the patient failed to show clinical improvement; a bacteremia reoccurred later and at autopsy it was found that the patient had developed a pneumococcus endocarditis.

It is interesting to note that in none of the patients with a decreasing number of pneumococci in the blood stream and recovering from the infection the initial bacterial count exceeded 30 colonies per 1 cc. of blood. Considering the possible technical errors in adding the exact amount of 1 cc. of blood to the agar plate, this figure confirms what Rosenblueth² reported previously: "We have not seen recovery in any serum untreated patient with more than 28 colonies per 1 cc. of blood." The experience that none of the patients with more than 30 organisms in the blood stream survives suggests that at least in the stage where the organisms enter the blood stream the number of organisms rather than variations in the virulence of the individual strains plays the major part in breaking down the resistance of the patient. Such consistence in the maximum degree of bacteremia which a patient can overcome could not exist if the virulence of the pneumococci would differ materially. This observation substantiates experimental findings of Whittle⁵ and of Gundel and Wasu,⁶ who tested the virulence of pneumococcus strains recovered from the sputum and empyemas of Types I and II lobar pneumonias. They found that such pneumococci are uniformly highly virulent. The relationship of the number of bacteria in the blood stream to resistance suggests further that the active factor, leading to the fatal outcome, is not an exotoxin, but either a so-called endotoxin or toxic products derived from the action of pneumococci upon body tissues.

TABLE 3.—RELATION OF STAGE OF PNEUMONIA, WHEN BACTEREMIA WAS FIRST DEMONSTRATED TO TREND OF BACTEREMIA.

	Bacteremia first demonstrated after onset of pneumonia.	
	Within 1 to 3 days.	After 3 days.
Number of patients with { Increasing bacteremia .	6	14
Decreasing bacteremia .	12	1

TABLE 4.—DISTRIBUTION OF PNEUMOCOCCUS TYPES AMONG PATIENTS SHOWING AN INCREASING AND DECREASING BACTEREMIA.

	Pneumococcus types.		
	I.	II.	IV.
Number of patients with { Increasing bacteremia .	10	9	1
Decreasing bacteremia .	2	10	1

When the patients are listed according to the stage of disease at admission to the hospital it is found that a bacteremia with an increasing number of bacteria occurs more often after the third day of disease, while the patient, who has a decreasing bacteremia has the bacteremia in the early stages of the disease. Type I pneumococcus showed more tendency to increase than to decrease in our series. However, all these factors are less constant and of lesser value for predicting a prognosis than a determination of the degree of bacterial invasion and its trend. In most patients with a positive blood culture and a bacterial count below 30 organisms per 1 cc. of blood a second blood culture taken within 24 hours after the first one indicates clearly the change in the degree of bacteremia.

Summary. 1. The degree of bacteremia and its course have been determined by a simplified repeated blood culture method in a number of pneumococcus pneumonia patients, not treated with antipneumococcus serum. The method employed requires 3 cc. of blood and gives results within 16 hours, if the degree of bacteremia is one or more organisms per 1 cc. of blood.

2. Of 20 patients who had an increasing or stationary degree of bacteremia none survived.

3. In the series of 12 patients in whom the bacteremia decreased and disappeared 10 recovered.

4. In none of the patients who overcame the infection did the maximum degree of bacteremia exceed 30 organisms per 1 cc. of blood at any time.

BIBLIOGRAPHY.

1. Sutton, A. C., and Sevier, C. E.: Johns Hopkins Hosp. Bull., 1917, 28, 315.
2. Rosenblueth, M. B.: J. Am. Med. Assn., 1928, 90, 1351.
3. Mellon, R. R., Acree, C., *et al.*: J. Inf. Dis., 1921, 29, 1.
4. Cole, R. I., and Moore H. F.: J. Exp. Med., 1917, 26, 537.
5. Whittle, C. H.: J. Path., 1927, 30, 569; and J. Hyg., 1928, 27, 412.
6. Gundel, M., and Wasu, Ch.: Z. f. Hyg. u. Infektionskrankh., 1931, 112, 436.

INTERNAL DRAINAGE.

A FACTOR IN THE PRODUCTION OF POSTOPERATIVE MASSIVE
COLLAPSE OF THE LUNG (PULMONARY ATELECTASIS).
SUGGESTIONS AS TO PREVENTION AND TREATMENT.

BY WILLIAM B. FAULKNER, JR.,*

ASSISTANT CLINICAL PROFESSOR OF SURGERY, UNIVERSITY OF CALIFORNIA MEDICAL
SCHOOL; VISITING SURGEON, UNIVERSITY HOSPITAL,

AND

EDWARD C. FAULKNER,†

ASSOCIATE IN THORACIC SURGERY, ST. MARY'S HOSPITAL,
SAN FRANCISCO, CALIF.

ANY theory which is offered to explain the production of post-operative massive collapse of the lung must account satisfactorily for the varied onset of the condition, diversity of signs and symptoms, predilection of sites, extensiveness, migrations, recurrences and response to various treatments.

The study of atelectasis as it has occurred both following and independent of surgical procedures leads us to believe that the cause and entire clinical picture can be explained on a combined mechanical and infectious basis. It is due to the presence of excess intrabronchial secretions and the influence of "internal drainage" upon these secretions.

By internal drainage, we mean the spilling of material from place to place within the tracheobronchial tree. Such spilling actually occurs, follows definite laws, spreads infection, obstructs bronchi and interferes with the air flow to the lung. This has been proved repeatedly by physical examination, Roentgen ray, iodized oil injection, bronchoscopic inspection, operative findings and autopsy examination¹ Figs. 1 to 4.

The sites at which the intrabronchial secretions collect, manifest abnormal physical findings and produce pulmonary atelectasis are dependent on: the amount, virulence and viscosity of the secretions; the relative position of the various bronchial openings; the course of the bronchial stems; the posture of the patient; and the length of time that the patient remains in a given position.

Source of Excess Intrabronchial Secretions. In patients with pulmonary tuberculosis, asthma, bronchiectasis and pulmonary abscesses, excess secretion or exudate is already within the trachea and bronchi before any type of surgical intervention is instituted; but in those who have had no previous pulmonary disease, the secretions are aspirated from the mouth and nasopharynx dur-

* From the Department of Surgery, University of California Medical School.

† From the Thoracic Surgical Department of St. Mary's Hospital.

ing and immediately following the operation. This aspiration is more common than is generally supposed and can occur with all types of anesthesia or even in the unanesthetized.

Evidence of Aspiration. Contrary to general opinion, the cough reflex is rather inefficient in prohibiting the entrance of foreign material into the trachea and bronchi; for iodized oil can be introduced through the mouth into the lungs of unanesthetized patients, and lipiodol instilled into the nares during sleep is found in the bronchi on Roentgen examination the following morning.² The observations of Mandelbaum,³ which were confirmed by us, add further evidence regarding the frequency of aspiration in the unanesthetized. He noted on bronchoscopic examination that the bronchial mucous membrane was definitely stained after dye had been introduced into the nares of wide awake and unanesthetized patients 8 to 10 hours previously. The high incidence of aspiration during general anesthesia is proven convincingly by the experimental and clinical studies of Lemon⁴ and Myerson.⁵ Seventy-nine per cent of Myerson's cases had blood in the trachea or bronchi following tonsillectomy even though the average duration of the operation was 9 minutes.

In 2 patients who had been operated upon in the sitting position under ether anesthesia for the relief of paranasal sinus conditions, we found blood in the bronchi of both lungs but especially the right. This material had drained down from the operative area, and had it not been removed, probably both of these patients would have developed atelectasis or other pulmonary complications; for considerable data have accumulated which show the rôle that increased intrabronchial secretions or materials play in the production of post-operative pulmonary atelectasis.

Evidence that Increased Intrabronchial Secretions Cause Atelectasis. In addition to Jacobaeus,⁶ reports of atelectasis following the introduction of iodized oil into the bronchi and after pulmonary hemorrhages, we have noted that the condition is not uncommon in unoperated and unanesthetized patients with pulmonary abscesses. In our cases, the atelectasis occurred at the area to which the pus could most readily spill by internal drainage. A right basal abscess produced a left-sided atelectasis when the patient lay on the left side for a period of time; but upper lobe abscesses led to atelectasis at the corresponding bases when the patient was in the semi-Fowler position. The part that increased intrabronchial secretions and exudates played in the production of the atelectasis was demonstrated clearly on bronchoscopic examination, for pus was found in the bronchi leading to the atelectatic areas, and the atelectasis disappeared as soon as the pus was removed.

In these patients with iodized oil injections, pulmonary hemorrhages and pulmonary abscesses, the onset of the atelectasis, as well as the symptoms, physical findings, roentgenologic changes.

bronchoscopic findings and response to treatment was essentially the same as that seen in the type of atelectasis that follows surgical procedures. Both the surgical and the nonsurgical atelectases were due to one of the following types of bronchial occlusion: thick plugs of inspissated pus, films of viscid mucoid material, inflammatory edema, or thin secretions that had run deeply into and filled the minor bronchial stems. Our observations lend support to the work of Elliott and Dingley,⁷ Coryllos and Birnbaum,⁸ Jackson and Lee,⁹ and Julian Moore.¹⁷

Previously, too much emphasis was placed on the importance of the thick plugs, and not enough attention was given to the other types of bronchial occlusion. In this respect, Sante¹⁰ reports a case of atelectasis that is worthy of mention because on first sight, it appears to be due to a cause other than bronchial obstruction. His opinion was based on the fact that the condition cleared up completely after postural drainage even though no bronchial plugs had been seen on bronchoscopic examination and no improvement had followed the bronchoscopic treatment. The sequence of events can be understood in this instance when we appreciate that atelectasis can be caused by thin secretions that run deeply into the minor bronchial stems. This type of material cannot be seen on bronchoscopic examination but can be spilled out of the small bronchi by postural drainage. We have proved this experimentally, and Julio Diez¹¹ has confirmed it on autopsy examination. In Diez's cases of postoperative atelectasis, plugs were found in the minor bronchial ramifications when not seen in the major bronchial stems.

With the bronchoscope in place, it has been observed that secretions can alter in both form and position either spontaneously or following cough and postural drainage exercises. We have seen viscid filmy secretions, that were occluding a bronchial opening, break loose suddenly from their attachments to the upper bronchial wall and retract like an elastic band into an apparently innocent and insignificant position on the floor of a larger bronchus. This unplugging of the bronchus and reestablishment of the air flow took place in spite of the fact that nothing was expectorated.

With this understanding of the behavior of intrabronchial secretions and the types of bronchial plugging, we are now in a position to discuss the clinical phases of postoperative atelectasis.

Postoperative Atelectasis. *The Onset and Severity of Symptoms.* The obstruction of the bronchial openings by secretions is more or less a matter of chance; for it may not occur at all or it may take place during any phase of respiration. If a large bronchus is occluded at the end of expiration when the lung is already diminished in air content, there will be a rapid onset of the atelectasis, sudden and marked reduction in the vital capacity, marked increase in the negative intrapleural pressures, retraction of the mediastinal structures toward the involved side and the production of serious and alarming



FIG. 1.—Iodized oil introduced through the mouth into the tracheobronchial tree without the use of any type of anesthesia. Note the bulk of the oil in the right lung.

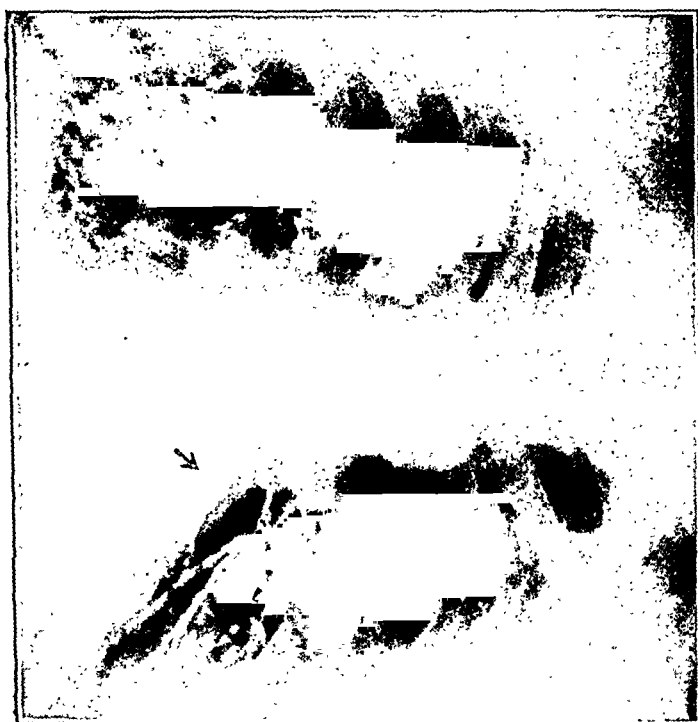


FIG. 2.—Internal drainage. Same patient as Fig. 1. The oil spilled from the right lung into the left after the patient lay on his left side for a few minutes. Posture determined this spilling. There was no cough and none of the oil was expectorated.

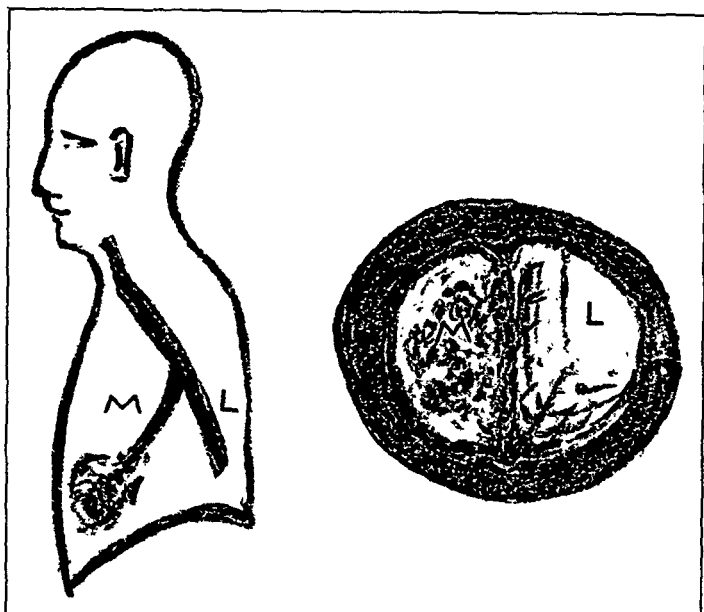


FIG. 3.—Sketch of a middle lobe abscess and the bronchoscopic appearance when the patient is in the erect position. The middle lobe bronchus (M) runs anteriorly while the lower lobe bronchus (L) passes posteriorly. There is neither adequate drainage of pus or spilling into the lower lobe bronchus when the patient is in this position.

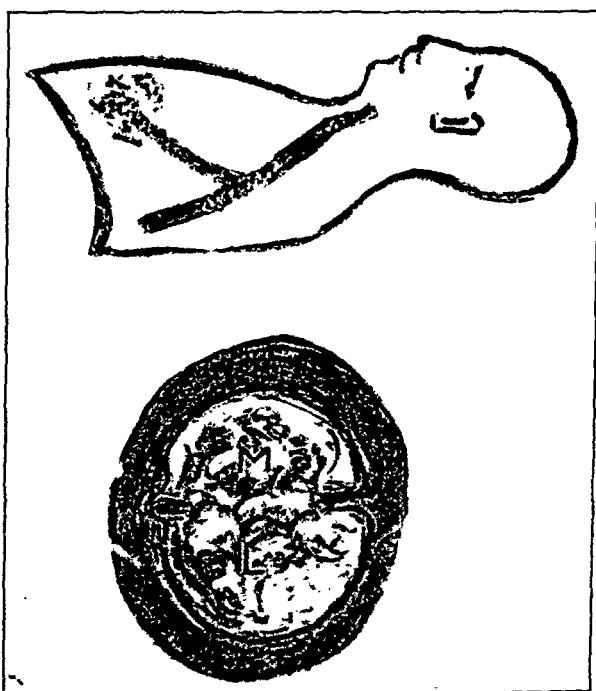


FIG. 4.—Internal drainage. Note the changed conditions when the patient lies flat on his back. The pus now spills from the middle lobe bronchus (M) to obstruct the air flow to the lower lobe bronchus (L). This mechanical spilling following changes in posture is important not only in lung abscesses but also in considering the migrations, recurrences and treatment of atelectasis.

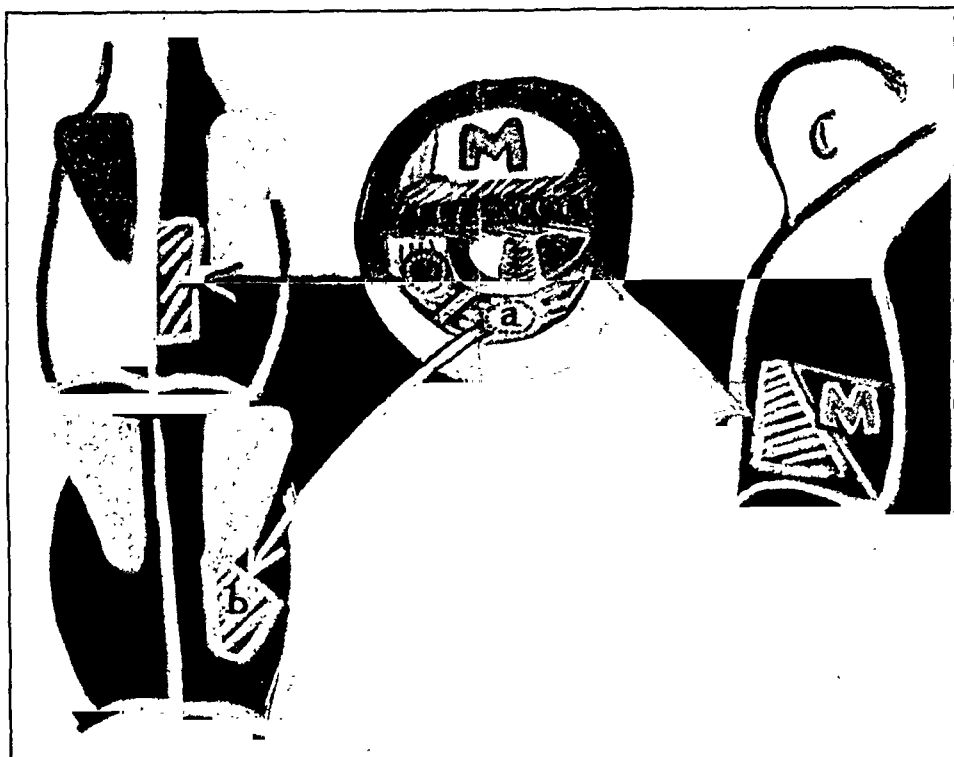


FIG. 5.—Diagram showing the minor bronchial openings of the right lower lobe which are most frequently obstructed by aspirated secretions, and the corresponding areas upon the chest where abnormal physical signs are elicited. (b) The most frequent site of atelectasis and (a) the posterior minor bronchus that supplies this area. (M) middle lobe.

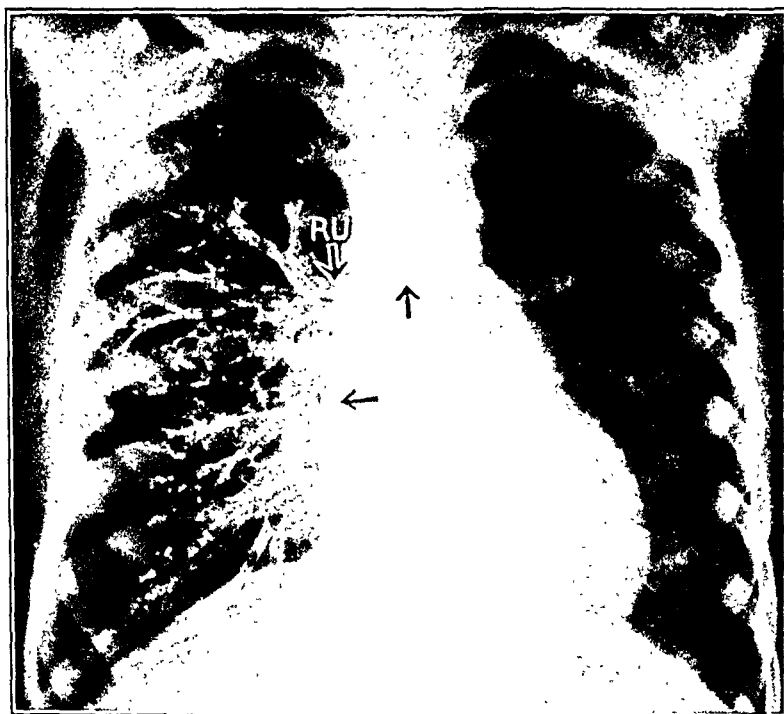


FIG. 6.—Lipiodol injection of the right lung. The upper lobe bronchus (RU) arises at an angle of 90 degrees from the side wall of the main stem bronchus; and if secretions are to flow into this lobe, the patient must be lying flat on his right side.



FIG. 7.—Specimen illustrating the anatomy of the tracheobronchial tree, the free communication between the bronchial trunks, and the opportunities for the spilling of intrabronchial material from one trunk to another. Atelectatic migrations take place in this manner. *T*, trachea; *RU*, right upper lobe bronchial opening directly across from the bifurcation of the trachea (*C*); *R*, right main bronchus; *L*, left main bronchus; *Sm*, septum between the middle and right lower lobe bronchial openings; *S*, septum between the left upper (*LU*) and left lower lobe bronchial openings (*LL*).

symptoms. Should the bronchus be plugged at the end of inspiration, however, an obstructive emphysema ensues first and the onset of the atelectasis is gradual and delayed depending on the rate of absorption of the trapped air. Accordingly, the symptoms are more gradual in onset and decidedly less severe.

The symptoms are no exact guide to the extensiveness of the atelectasis but are determined by the suddenness and amount of reduction in the vital capacity and the severity of the associated intrabronchial infection. A gradual reduction in the vital capacity, even though of high degree, can be tolerated much better than a less marked but more sudden alteration. This is particularly applicable to those patients with extensive atelectasis and practically no symptoms.

It is the occasional suddenness of the onset and the similar type of recovery that have led to the suggestion that the etiologic factors were on a vasomotor, phrenic, vagus, or sympathetic reflex basis; but these theories have never been proved and we have found no evidence to support them. Likewise, the early suggestion of Pasteur¹² that the elevation of the diaphragm was responsible for the atelectasis is now abandoned, for the high diaphragm is a result and not a cause of the condition. The atelectasis in Pasteur's cases, appears to us, to be explained best on a basis of aspiration and the internal drainage of these aspirated secretions throughout the lungs; because his deductions were based on the study of debilitated patients suffering from postdiphtheritic paralyses. These are the types most likely to aspirate material and least likely to expectorate it.

Type and Extensiveness. As has been shown in discussing the behavior of intrabronchial secretions, thin material enters the minor bronchial openings and produces a patchy or lobular atelectasis; whereas, the thicker more viscid material is likely to plug a larger bronchus and produce a lobar atelectasis.

Predilection of Sites. It is interesting to note the regularity with which postoperative atelectasis occurs at certain sites and to find that these areas are identical with those at which lipiodol, blood and pus collect when the patient is in a given position. The influence of posture in predetermining the site of the atelectasis is shown especially following operations upon the kidney. In such cases, when postoperative pulmonary complications occur, they involve the lung that is opposite from the side of the diseased kidney. On first sight, this appears to support Briscoe's¹³ theory of compression of the chest wall and interference with the muscles of respiration as the primary factor in the production of atelectasis; but we believe that the compression of the chest wall is a contributing rather than a primary factor and that the atelectasis will not occur if excess secretion is not present within the tracheobronchial tree. The aspirated secretions spill into the lung that is in a dependent position during and following the operation and account for the atelectasis

at a particular site. The same principle applies following operations upon the chest. The atelectasis does not necessarily occur on the side that is tightly strapped and on which there is an interference with the muscles of respiration, but rather at the site to which the collected secretions drain and obstruct bronchi. By the compression theory, it would be difficult to explain the incidence of atelectasis at the right base especially when the operation is upon a distal portion of the body and when there is no compression of the chest wall or interference with the muscles of respiration.

The frequency of involvement at the right base is due in fact to the anatomical features which render this bronchus accessible to secretions, and to the semi-Fowler or elevated postoperative posture which permits the drainage into the lower lobe. Bradford¹⁴ has called attention to the frequency of minor degrees of atelectasis at the area lying below the angle of the right scapula. This is easily understood. The first available opening reached by small amounts of thin aspirated material is the posterior minor bronchus of the right lower lobe, and this leads to the area described by Bradford (Fig. 5).

The inability of intrabronchial secretions to flow into the upper lobe bronchial openings when the patient is in the semi-Fowler position accounts for the infrequency of isolated upper lobe involvements. All of the cases of isolated right upper lobe atelectasis that we have seen were in the supine position and usually lying upon the right side. In other words, they were in the position that facilitated best the spilling of secretions into this upper lobe. If the right upper lobe is to become involved, the patient must be in the same position that is employed when filling this lobe with lipiodol (Fig. 6). The same general principles apply to bilateral basal atelectases.

Migrations and Recurrences. The spilling of intrabronchial secretions by internal drainage accounts also for the types of atelectasis that show migrating and recurring tendencies (Fig. 7). When patients with right upper lobe atelectasis are changed from the supine to the semi-Fowler position and instructed to take deep breaths, the signs of the atelectasis disappear from the upper lobe and begin to appear over the corresponding lower lobe. We have seen migrations not only from the upper lobe to the base, but also from the right lower to the right upper, and from the left lower to the right upper lobe when the patient assumed the proper posture to permit spilling in these directions.

Should the patient's original position be reassumed after the migration has taken place, the secretions can return to their former position, reobstruct the bronchial openings and produce a recurrence of the atelectasis.

Occasionally infection plays a rôle in these recurrences. Highly virulent aspirated material causes an inflammatory edema of the bronchial opening where it lodges; and although a postural change

may permit the evacuation of the pus and a temporary disappearance of the atelectasis, the continuance of the infection and the increase in the localized bronchial edema lead to a later occlusion of the same bronchus and a reestablishment of the atelectasis at the original site. There are no just grounds for classifying this edema on an angioneurotic basis; and we cannot agree with those who believe that angioneurotic edema is a factor in the usual type of postoperative atelectasis.

Sante Maneuver and Spontaneous Cures. The occasional spontaneous cures without treatment and the success of the Sante maneuver are dependent on this same principle of internal drainage which permits secretions to spill away from the occluded bronchus and allows air to enter the previously involved lung. As has been pointed out, it is not necessary to expectorate this material in order to get relief, but as long as complete expectoration does not take place, there is always the danger of a recurrence or migration.

Influence of Anesthetic Agent. When it is remembered that aspiration can take place in the unanesthetized as well as in the anesthetized, it is not surprising that postoperative atelectasis occurs following all types of anesthesia. The facilities offered for aspiration and the inability to expectorate play the more important rôle, but the postoperative duration of the narcosis is also important; and for these reasons, we should avoid those anesthetics which leave the patient irrational, uncoöperative and unable to expectorate for hours after his return to the ward.

Prevention and Treatment. Success in the management of these cases depends upon the strictest attention to detail not only during the operation but also before and afterward. Therefore, measures should be instituted to decrease the amount and virulence of the mouth secretions, to prevent aspiration, and to maintain the normal air flow to the lung.

Terry¹⁵ has shown clearly that both the incidence and seriousness of postoperative pulmonary complications could be lessened decidedly merely by the treatment of faulty mouth hygiene in general surgical cases during the 12 hours preceding the operation.

The preliminary management of general surgical cases is altered somewhat when there is an associated pulmonary disease such as chronic bronchitis, asthma, bronchiectasis, pulmonary tuberculosis or pulmonary abscess. In such cases, apart from the nature of the surgical procedure, it is advisable to treat the patient bronchoscopically before the operation so as to empty the bronchi and prevent the spilling of pus and secretion throughout the lung. Otherwise, it will be almost impossible to escape the spread of the pulmonary disease and the obstruction of the bronchi leading to previously uninvolved areas. The bronchoscopy can be performed under local anesthesia in from 1 to 3 minutes and under such circumstances it is not a trying procedure for the patient. Whenever

thoracoplasties, paraffin fillings, or pulmonary cautery operations are contemplated, the emptying of the bronchi is absolutely indicated; because during the chest operation, pus is squeezed out of the diseased area and if this is not expectorated or mechanically removed, a postoperative pulmonary complication will be almost inevitable. It is such a mechanism that explains the spread of tuberculosis to the base of the same lung or into the contralateral side following thoracoplastic operations. As discussed in a previous paper,¹⁶ many of these factors play a prominent rôle in the cause of death following operations upon the lung.

The posture of the patient during and following the operation is very important. It should be such as to prevent the drainage of material into the bronchi. In general, the Trendelenburg position is to be recommended; and the erect or semi-Fowler posture is to be reserved for the exceptional case. The Fowler position should be prohibited also in patients who are vomiting or undergoing gastric lavage, for these are the occasions at which aspiration can take place most readily.

General anesthesia is not contraindicated if it is so given that the patient awakens immediately following the completion of the operation. Scopolamin and morphin (twilight anesthesia), amytal and avertin do not fall into the approved list of anesthetics, because the postoperative period of narcosis is so long that it interferes with the expectoration of the aspirated intrabronchial secretions. For thoracoplastic operations, the anesthesia employed by Ziegler is ideal. He dispenses with all preliminary narcotics and sedatives and uses local throughout the entire operation. This permits expectoration at all times. Graveson employs a very light ether anesthesia along with local; but he insists on the patient expectorating thoroughly before leaving the operating table. The low incidence of the postoperative spread of pulmonary disease in his cases speaks well for this method.

We must now consider the occasional patient who develops severe respiratory difficulty on the operating table at a time when the anesthesia is so deep that expectoration is impossible and when the removal of mouth secretions fails to give relief. For the past 5 years, we have made bronchoscopy a routine procedure in such instances and have had very gratifying results. Our first patient of this type developed difficult breathing and very loud rhonchi just before the completion of a hysterectomy under ether anesthesia, and it seemed almost certain that a postoperative pulmonary complication would ensue. The bronchoscope was employed at once; and thick mucoid material was found in and removed from the pharynx and trachea. The respiratory difficulty was relieved immediately and the patient made a strikingly uneventful convalescence. In a second patient whose condition was less alarming but in whom very definite rhonchi were present, considerable viscid

material was expectorated following the postoperative employment of the Trendelenberg position. This patient's convalescence was similarly uneventful. The decision as to whether the bronchoscope or postural drainage is to be used in the individual case must rest upon the judgment of the surgeon and the facilities at hand; but in urgent cases, bronchoscopy offers the quickest and surest means of relief. In both of the above cases, the secretions which were removed from the bronchi were the same as those which are seen so often in the mouth of anesthetized patients. This should sufficiently emphasize the importance of keeping the mouth and pharynx free of excess saliva if aspiration and postoperative pulmonary complications are to be prevented.

Much has been written concerning the danger of using atropin if atelectasis is to be prevented; but we have found no contra-indication to its pre-operative use if the bronchi are free of exudate, because by diminishing the amount of secretion, the opportunities for aspiration are minimized. We do not use it before lung operations, however, nor after the rhonchi appear, because rational treatment demands the removal and not the thickening of the intrabronchial secretions. Postoperatively, we look with disfavor upon atropin but prefer the administration of expectorants.

Pure carbon dioxid inhalation has proved of value both in the prevention and treatment of postoperative pulmonary complications, because it causes hyperventilation and deetherizes the patient. The inhalations are given on the operating table in the Trendelenburg position at the end of the operation and are repeated 3 or 4 times daily for the first 2 days postoperatively. The amount of gas given should be sufficient to stimulate deep rapid breathing but it should not be carried on to the point of fatigue. What has been said previously concerning posture applies equally well during the carbon dioxid inhalations, for the aim should be to allow the secretion to drain out of and not deeper into the bronchi. We warn again against the general use of the semi-Fowler position; this hinders adequate drainage and increases the seriousness of the patient's condition. Correct posture depends on the site of the atelectasis and is determined on anatomical grounds in keeping with the principles of internal drainage.

For general use postoperatively, we can recommend Sante's method of rolling the patient from side to side; but patients that do not respond to these measures are to be bronchoscoped. This permits the removal of the intrabronchial secretions and the treatment of the edematous bronchial mucous membrane with cocain, adrenalin, ephedrin, or silver nitrate. The efficacy of the bronchoscopic treatments is increased if followed by postural drainage to empty the smaller bronchi that are beyond the reach of the bronchoscopic suction.

Conclusions. 1. The cause and entire clinical picture of postoperative massive collapse of the lung (pulmonary atelectasis) can be explained on a combined mechanical and infectious basis.

2. Postoperative pulmonary atelectasis is due primarily to the bronchial obstruction resulting from the presence of excess intra-bronchial secretion and the influence of "internal drainage" upon these secretions.

3. By "internal drainage" is meant the spilling of material from place to place within the tracheobronchial tree to spread infection, obstruct bronchi and shut off the air flow to a portion of the lung.

4. This spilling depends on the amount and viscosity of the secretion and the posture of the patient.

5. In certain pulmonary diseases, the excess secretions are already present within the tracheobronchial tree before the operation; but in other conditions, the secretions are aspirated from the mouth and nasopharynx during or immediately following the operation.

6. Internal drainage accounts for the varied onset of postoperative pulmonary atelectasis, diversity of symptoms, predilection of sites, extensiveness, migrations, recurrences, and the response to various treatments.

7. We do not believe that vasomotor, phrenic, vagus or sympathetic reflexes, angioneurotic edema or compression of the chest wall are primary etiologic factors in postoperative atelectasis.

8. Careful attention to the mouth hygiene, the posture of the patient during and following the operation, the prevention of aspiration and the removal of intrabronchial secretions should either prevent atelectasis and other postoperative pulmonary complications or decidedly lessen the frequency of their occurrence.

9. Postural exercises, carbon dioxid inhalations and bronchoscopic treatments have proved of value in the management of patients with postoperative atelectasis when carried out in accordance with the principles of internal drainage.

BIBLIOGRAPHY.

1. Faulkner, William B., Jr.: *Internal Drainage: Its Application in Pulmonary Suppuration*, J. Am. Med. Assn., 1930, 95, 1325.
2. Quinn, Lester H., and Meyer, Ovid O.: *The Relationship of Sinusitis and Bronchiectasis*, Arch. Otolaryngol., 1929, 10, 152.
3. Mandelbaum, M. J.: *Personal Communication*.
4. Lemon, W. S.: *Aspiration; Experimental Study*, Arch. Surg., 1926, 12, 187.
5. Myerson, M. C.: *Pulmonary Aspects of Tonsillectomy Under General Anesthesia*, Laryngoscope, 1922, 32, 929.
6. Jacobaeus, H. C., Selander, G., and Westermarck, N.: *A Study of Acute Massive Collapse of the Lung*, Acta med. scand. (Stockholm), 1929, 71, 439.
7. Elliott, T. R., and Dingley, L. A.: *Massive Collapse of the Lungs Following Abdominal Operations*, Lancet, 1914, 1, 1305.
8. Coryllos, P. N., and Birnbaum, G. L.: *Bronchial Obstruction: Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia*, Am. J. Roentgenol. and Rad. Therapy, 1929, 22, 401.
9. Jackson, C., and Lee, W. E.: *Acute Massive Collapse of the Lungs*, Trans. Am. Surg. Assn., 1925, 43, 723.
10. Sante, L. R.: *Massive Collapse of the Lung*, Radiology, 1927, 8, 1.

11. Diez, Julio: Personal Communication.
12. Pasteur, W.: Respiratory Paralysis After Diphtheria as a Cause of Pulmonary Complications, with Suggestions as to Treatment, *AM. J. MED. SCI.*, 1890, **100**, 242.
13. Briscoe, J. C.: The Mechanism of Postoperative Massive Collapse of the Lungs, *Quart. J. Med.*, 1919-1920, **13**, 293.
14. Bradford, J. R.: Massive Collapse of the Lung as a Result of Gunshot Wounds, with Especial Reference to Wounds of the Chest, *Quart. J. Med.*, 1918-1919, **12**, 127.
15. Terry, Wallace I.: Personal Communication.
16. Faulkner, William B., Jr.: Internal Drainage: A Newer Conception of the Cause of Postoperative Death of Patients with Pulmonary Abscesses, Bronchiectasis and Pulmonary Tuberculosis. Suggestions as to Prevention, *Am. J. Surg.*, 1931, **12**, (new series), 27.
17. Moore, Julian A.: Post-operative Pulmonary Atelectasis, *J. Michigan Med. Soc.*, 1930, **29**, 182.

AN ANALYSIS OF 312 CASES OF DIABETES TREATED IN AN OPEN HOSPITAL IN EIGHT YEARS.

BY ROLAND N. KLEMMER, M.D.,

LANCASTER, PA.

(From the Medical Service of the Lancaster General Hospital.)

THIS report is based on a review of all the diabetic patients treated at the Lancaster General Hospital during the first 8 years during which insulin was available for general use. The Lancaster General Hospital (265 beds) is "open" to all physicians of the county, and each physician is permitted to treat his own private patient. The 312 cases reported were treated by 47 different medical men. Although the majority of the patients were under the care of a few physicians, a considerable number of patients were treated by physicians who see only a relatively few cases of serious diabetes and whose experience in this field was consequently limited. There is a natural tendency for medical literature to contain many more reports of successful therapy than of unsatisfactory therapy, but we felt that, especially in diabetes, there were just as many lessons to be learned from the errors of treatment as from the successes. Consequently we have freely discussed both.

In the 8 years a total of 312 cases were treated, of whom 43 (13.7 per cent) died before leaving the hospital (Table 1). There were 194 females and 118 males. The total cases were separated into: (1) Surgical, those who had some form of operation, not including extraction of teeth; and (2) medical, including all the unoperated cases.

There were 59 operative cases, with 9 deaths, a mortality of 15.2 per cent. During the 8 years 19 per cent of all the patients admitted with diabetes underwent some surgical procedure. The reasons for operation and causes of death are listed in Table 2.

TABLE 1.—ANALYSIS OF CASES.

Year	Total No. patients.	No. of operations.	Percentage of operations.	No. of deaths.			Av. No. days surgical cases in hospital.	Av. No. days medical cases in hospital.
				Med.	Surg.	Total.		
1923 to 1924	36	6	16.7	3	2	5	36	19
1924 to 1925	36	6	16.7	5	2	7	27	24
1925 to 1926	38	7	18.4	5	0	5	19	14
1926 to 1927	45	11	24.4	5	0	5	27	10
1927 to 1928	28	3	10.7	6	1	7	20	10
1928 to 1929	32	7	21.9	2	0	2	29	43
1929 to 1930	31	2	6.5	2	0	2	15	20
1930 to 1931	66	17	25.8	6	4	10	32	15
Totals for 8 years	312	59	18.9	34	9	43	26	19

TABLE 2.—SURGICAL CASES—LIST OF OPERATIONS.

Operation.	No. of cases.	No. of deaths in hospital.
Amputation of one or more toes	3	
Amputation through foot	1	
Amputation of leg	13	3
Amputation of thigh	5	1
Amputation of fingers	1	
Bone curettage	1	
Open reduction—fracture of patella	1	
Cataract extraction	2	
Tonsillectomy	4	
Thyroidectomy	2	
Laparotomy (exploratory)	1	
Cholecystectomy	3	1
Appendectomy	1	
Hysterectomy	3	2
Suprapubic cystotomy	1	
Cervical polyp excised	2	
Abscesses incised	6	
Carbuncles	6	
Abscess of liver	1	1
Amputation of breast	1	
Colostomy	1	1
Total for 8 years	59	9

In the 253 medical cases there were 34 deaths (13.5 per cent mortality). The medical complications are listed in Table 3. Under the classification of coma are included only those cases which were apparently primary diabetic coma, *i. e.*, not secondary to some other disease or infection, such as pneumonia, septicemia, etc. The number of cases on this list is rather large because in most of these cases autopsies were not permitted. We believe that if all these cases had been autopsied the number under this classification would be much smaller, due to the discovery of various unexpected lesions, such as abscesses of the kidney and the like.

Turning to the amount of insulin used in treatment (Table 4), we found that the surgical cases during their stay in the hospital

took approximately the same amount as the nonsurgical cases, but on discharge the insulin dosage of the surgical cases was a little higher than the medical, probably due to the temporarily decreased sugar tolerance caused by the condition operated upon—frequently an infection. In comparing the dosages of insulin in the first year of this series with that of the last year, one notes the striking increase in amount of insulin per patient. However, this marked difference, on closer inspection, is seen to exist merely between the first year and the latter 7. It is due undoubtedly to early timidity in using the larger doses.

TABLE 3.—MEDICAL COMPLICATIONS.*

Complications.	No. of cases.	No of deaths in hospital.
Coma (without surgical complications)	27	22
Infection—toes	17	
Infection—foot	7	1
Acute bronchitis	1	
Pleurisy	1	
Pneumonia	3	1
Pulmonary tuberculosis	2	
Carbuncle	3	1
Cystitis	1	
Septicemia	2	2
Otitis media	2	
Corneal ulcer	1	
Syphilis	2	
Arthritis	1	
Catarrhal jaundice	1	
Acute cholecystitis	1	
Chronic cholangitis	1	
Cholelithiasis	1	
Nephritis	4	1
Cerebral hemorrhage or embolism	5	5
Fracture of femur	1	
Compound fracture of fibula	1	
Dry gangrene—lower extremity	3	
Toxic thyroid	1	
Hypothyroidism	1	
Hypoglycemia	2	
Alcoholism	2	
Hemochromatosis	1	
Ruptured appendix	1	1
Total for 8 years	96	34

* If more than one complication existed in the same patient, only the most important one is listed.

TABLE 4.—MAXIMUM DAILY DOSAGES OF INSULIN.

Year.	Average of surgical cases, units.	Average of medical cases, units.	Average of total cases, units.
1923 to 1924	20	18	19
1924 to 1925	44	33	38
1925 to 1926	54	35	45
1926 to 1927	39	43	41
1927 to 1928	48	46	47
1928 to 1929	35	40	38
1929 to 1930	26	48	37
1930 to 1931	45	72	59

TABLE 5.—DAILY INSULIN DOSAGE ON DISCHARGE.

Year.	Average of surgical cases, units.	Average of medical cases, units.	Average of total cases, units.
1923 to 1924	7	13	10
1924 to 1925	27	25	26
1925 to 1926	41	24	32
1926 to 1927	27	22	24
1927 to 1928	32	18	25
1928 to 1929	6	17	12
1929 to 1930	22	28	25
1930 to 1931	30	25	27

As would be expected, the average hospitalization of the surgical cases was longer than that for the medical (Table 1). For the 8 years surgical patients averaged 26 days in the hospital and medical, 19 days.

Uniformly Good Results in All Mild Cases. The moderate and mild cases of diabetes obtained uniformly good results. The only requirement was that the diet be somewhat restricted in carbohydrate although containing sufficient calories. Insulin was used frequently in small doses but occasionally was not necessary. Corresponding to the general trend in most diabetic clinics, the treatment in this hospital has swung from the starvation type of diet, with a minimum of insulin, to the free carbohydrate, more normal diet with free use of insulin if necessary. There are a number of advantages for this higher carbohydrate and higher total caloric allowance:

1. It is closer to the normal diet of the healthy person.
2. It permits keeping the patient at a normal weight and in perfect strength.
3. Since the patient is well nourished there is less temptation for "cheating" in the diet.
4. Finally, it is believed by some that the complete oxidation of fats, brought about by the abundant carbohydrate oxidation, lessens the likelihood of vascular sclerosis.

The disadvantages of this method are:

1. The greater expense of treatment due to the larger doses of insulin.
2. A certain number of patients, who otherwise could do without the injections, when on a high carbohydrate diet must be inconvenienced by taking insulin.
3. There is considerably more danger that patients on the high diet and high insulin régime may become careless and neglect the insulin suddenly—occasionally resulting in acidosis. For example, 2 of our cases after short periods of neglect of diet and insulin were admitted to the hospital in coma and died.
4. Hypoglycemic reactions (insulin shocks) are more common.
5. A serious objection is that, unless carefully controlled, the diabetic patient on liberal diet and insulin is liable to get fat—a dangerous thing in severe diabetes.

However, the experienced diabetic patient taking insulin soon

finds out that he can eat satisfying quantities of food by slightly increasing his insulin and physicians must always adapt their treatment to the conditions of the individual case.

Severe Cases, Comatose and Precomatose. In contrast to the uniformly good results obtained in all the mild cases of diabetes, the results in coma or precomatose patients in an open hospital were not so satisfactory. In the hands of those physicians particularly interested in diabetes, comatose patients were treated energetically by gastric lavage, enema, external heat, fluids by hypodermoclysis (or intravenously if patients were unable to swallow) and sufficient doses of insulin and glucose carefully controlled by urinary and blood sugar estimations and tests for acidosis. However, there is considerable room for improvement in the treatment of coma by the physician or surgeon who sees only an occasional case and does not appreciate the gravity of the condition.

Staff Coöperation for Adequate Treatment of Severe Diabetes. Because of inability to concentrate the treatment of diabetes under one service or under a diabetic team due to the very nature of an open hospital, our attempts to improve results have been directed mainly toward the further education of all physicians using the hospital in the proper management of diabetic coma. This is done mainly by a free discussion of cases at staff meetings. The results in improvement of treatment are gratifying. Another tendency which also develops with further education is that, although the mild diabetic is treated by everyone, the coma cases are more liable to be referred to those physicians who are known to treat considerable numbers of diabetic patients and who, therefore, are presumably more competent to treat the emergency of coma.

Because of the fact that patients will often delay all day and take decisive steps only toward nightfall in serious diabetes, it is frequently necessary to apply the first and most energetic diabetic treatment at night. It then becomes necessary not only for the staff physician to remain on duty all night, but he must have the coöperation of a trained laboratory worker. Usually the resident physician on laboratory service has been used at this Hospital. One of the regular laboratory technicians is also on call at night for such emergencies. The staff physician should intimately supervise and personally see the patient in coma at frequent intervals during the first 24 hours at least. The practice of some physicians to turn over patients in diabetic coma to the intern who is possibly theoretically well grounded, but often has had no practical experience with such cases, is certainly to be deplored.

The Treatment of Acidosis Is of Primary Importance. The elimination of acidosis is the first principle in the treatment of diabetic coma. Five medical cases suffering from various complications and 1 postoperative case were rescued from deep coma. The relatively small number of coma recoveries is partially due to the fact that in this series a diagnosis of coma was not made unless the

patient was entirely unconscious and could not be aroused. It is probably better usage to include in this group those patients who are merely drowsy or mentally sluggish and show large amounts of ketone bodies in the urine and a marked lowering of the plasma CO_2 . We have found instances of diabetic patients who were subjected to major operations without any estimations for the presence of acidosis. In all surgical cases the determination of the presence or absence of acidosis should be a routine procedure, not only before but also after operation. In some cases in this series, although the presence of acidosis had been definitely established by clinical and laboratory examinations, it was disregarded and attention concentrated on simply maintaining the blood sugar at a normal level—with disastrous results. One case of coma had a normal blood sugar level but laboratory tests showed marked ketosis at the time of death. Postmortem examination was negative, indicating that diabetic coma was the deciding factor. The condition which demands first attention is not the height of the blood sugar, but the state of acidosis as determined clinically by drowsiness, dry skin and mucous membranes, sweet odor of the breath, etc., and by the laboratory tests for acetone and diacetic acid in the urine and CO_2 in the blood and alveolar air. "Fats burn in the flame of the carbohydrate." The burning of carbohydrate is accelerated by insulin. Therefore, if the blood sugar is high, large doses of insulin may be safely employed to burn carbohydrate and consequently indirectly burn fatty acids. If the blood sugar approaches normal acidosis still persists, glucose must be supplied by mouth, intravenously or otherwise in order to provide an additional fuel for the burning of the rest of the fatty acids.

Insulin. Regarding the frequency of administration and total doses of insulin necessary there was tremendous variability. Depending on the difficulty in eliminating the acidosis, patients in coma received doses of from 20 units every 2 or 3 hours to 40 units every 15 minutes. One boy of 12 years required 360 units of insulin the first 24 hours to clear up the coma and was discharged in 36 days, taking no insulin whatever. A girl, aged 7 years, with measles and bronchopneumonia, required 750 units the first 24 hours and eventually recovered. A Hebrew patient, aged 65 years, with severe and extensive infection of the foot, required 100 units of insulin 3 times daily for a period of 4 days (April 28 to May 1, 1930), and he was not even in coma. Squibb's and Lilly's insulin were interchanged in this case and samples of the insulin used were sent to the Lilly Laboratory and potency verified at the time these doses were used. The fatal case of septicemia with bilateral renal abscesses received 1000 units of insulin in 6 hours, with practically no effect on the blood sugar.

Danger of Hypoglycemia in Diabetic Coma. If the blood sugar is brought too low (hypoglycemia) a very real danger is introduced. When coma cases are treated too energetically with insulin or by

large doses of insulin insufficiently checked by urinary and blood sugar estimations, a diabetic patient in coma may have hypoglycemia superadded to his primary disease and die without having had any lucid interval. It would seem probable that this happened in a comatose patient admitted with a blood sugar of 440 mg. per cent. Massive doses of insulin reduced the blood sugar to 30 mg. per cent and the patient died without having recovered consciousness. Unfortunately an autopsy was not obtained. Diabetic patients can sometimes live for days in comparative comfort with blood sugar level between 300 and 400, but when the blood sugar is reduced to 30 or 40 mg., unless glucose is promptly administered, survival is probably only a matter of hours.

Administration of Fluids in Coma. In the treatment of coma one must be certain that the fluids administered actually get into the body of the patient. One of the cases in the series exemplifies what may happen when this is not accomplished.

Case Abstract. CASE 1.—The patient was a girl, aged 13 years, known to have been diabetic for 7 months. Two days before admission she had headache and was drowsy. She was admitted to the hospital in coma at 10 P.M. During the next 4 hours she received 80 units of insulin and was given glucose solution by proctoclysis. At 2 A.M. the nurse's record states: "Patient vomited a large amount of dark green liquid and expelled the glucose solution from the bowel." At 2.10 A.M. she died.

Although an autopsy was not obtained, we may assume that part of the failure in treatment was due to the fact that although the patient was seriously dehydrated, the stomach and colon were distended by fluid which was not being absorbed. To insure effective action, the fluid should have been given in this case by hypodermoclysis or intravenously.

Importance of Infections. Every diabetic patient should be warned that any infection or, in fact, any condition which upsets the even tenor of his daily life should make him all the more careful of his diabetic regulations and visit his physician for even minor affections when in doubt. A common cold or hoarseness may be a signal of reduced sugar tolerance. Two cases will illustrate the more serious infections.

CASE 2.—A female patient, aged 56 years, was admitted in coma with a history of increasing drowsiness for the 2 days preceding admission. Her blood sugar was 516 mg., blood plasma CO_2 17 volumes per cent and the blood urea nitrogen 28 mg. She was given the usual recognized treatment for coma plus very large doses of insulin. Two hours after admission the blood sugar was 410 mg. She received 1000 cc. of normal saline by hypodermoclysis and 100 gm. of glucose in 1200 cc. of water intravenously during the 6 hours of treatment. Intravenously and intramuscularly, a total of 1000 units of insulin were administered during the 6 hours in the hospital but she died with a blood sugar at 520 mg. Autopsy disclosed a carbuncle of one kidney and scattered abscesses throughout the other. The colon bacillus was isolated on culture.

CASE 3.—Another patient, a female, aged 48 years, was admitted with a carbuncle on the lip. In spite of the fact that the blood sugar was persistently kept normal and acidosis was successfully combated, the patient died. Autopsy showed metastatic abscesses of the lungs and kidneys.

Both the preceding cases emphasize the importance of obtaining postmortem examinations in diabetic patients so that we "do not lose faith in insulin." In the first case the renal abscesses were entirely unsuspected antemortem and the case apparently was one in which insulin simply had no effect.

In the patients who suddenly developed diabetic acidosis without having had previous knowledge of a diabetic tendency there was usually found some severe precipitating infection, such as septicemia, pneumonia, carbuncle, etc. Conversely, when diabetic acidosis develops suddenly in a patient who has previously not been diabetic the prognosis must be more guarded than if the acidosis developed in a recognized diabetic patient. In the first-mentioned type of case a very diligent search for infection should always be made.

Although much larger doses of insulin are required when infections are present, the diabetic patient should not succumb to any infection which could be cured in his nondiabetic brother. The recovery of the 2 cases of pneumonia and the numerous severe peripheral infections are illustrative of the good results which are possible. In order to obtain the best results, all diabetic patients with severe infections must be hospitalized.

Hypoglycemia. Although diabetics with infections may require large doses of insulin, other patients may be thrown into hypoglycemia by apparently insignificant doses of insulin.

CASE 4.—An adult female, who had been receiving 10 units of insulin daily, one afternoon became very weak, perspired profusely and became stuporous. Ten teaspoonfuls of sugar in 4 ounces of orange juice and 5 minims of adrenalin were administered, but her condition became progressively worse. One and a half hours later it was necessary to give 20 cc. of 50 per cent glucose intravenously. The patient recovered.

Two cases were admitted to the hospital in hypoglycemic coma, "insulin reaction." Both occurred in 1930-1931 and both recovered. The notes on 1 case are interesting:

CASE 5.—The patient was a female, aged 35 years, who was comatose on admission, but blood sugar proved to be 25 mg. per 100 cc. She had been treated at the hospital 5 months previously for diabetic coma and at the time of discharge was taking insulin, 20 units, 3 times daily. It was learned that just previous to the present admission she had been very irregular in her diet and on the day of admission, although she had not felt well before dinner, she had taken the usual amount of insulin and eaten very little. She became unconscious soon afterward. This case illustrates both the danger of carelessness in diet and the importance of reducing the insulin dosage if little or no food is taken at a meal.

The importance of guarding against hypoglycemia in diabetic coma has already been mentioned.

Importance of the Adherence to Diet and Insulin. As other observers have already pointed out, we found that most of our cases of uncomplicated coma were due to negligence. Many of the patients who died in diabetic coma had been rescued from coma one or more

times previously. The 3 following cases illustrate the penalty of laxity on the part of the patient.

CASE 6.—A female, aged 20 years, had been known to have diabetes for 3 years. She had been negligent of the diet the last few days before admission and had stopped the use of insulin. The day before admission she was taken ill with nausea and vomiting. She died 36 hours after admission, although she received 510 units of insulin in the first 24 hours.

CASE 7.—Another patient was a male, aged 38 years. The resident physician's notes state: "Patient knew he had diabetes for 3 years. He was admitted to the hospital previously and put on diet and insulin. He kept to the diet fairly well and took insulin while at home. When away from home he was careless about the diet and insulin. Last week he was away and omitted insulin. When he returned he felt badly but refused insulin. On the morning of admission he was irrational." He died within 24 hours.

CASE 8.—The third case was a male, aged 58 years. Diabetes had been diagnosed 2 years previously. One year before final admission he was treated for carbuncle. The notes state: "He had a special diet to which he had not adhered recently. Had gone to an 'electrical doctor' who told him he had cured his diabetes and that he should eat bread and potatoes. He was well until 2 days ago." He died in coma.

Surgery in Diabetes. One should never underestimate the risk in operating upon a diabetic patient. One patient had a leg amputation for gangrene and did not even require any insulin; another had an uncomplicated tonsillectomy and was comatose for 4 days before recovery; a third patient underwent thyroidectomy and was discharged on the fourteenth day with attention to diet alone and without having required any insulin.

It is especially important to control acidosis after surgery rigidly. Probably, if the acidosis could have been controlled following a leg amputation in 1 of our patients, the secondary thigh amputation would not have been required.

Another point of great importance in surgery, especially of the lower extremities, is the exact differential diagnosis between inflammation and necrosis or actual gangrene. Inflammatory cases, even if extensive, can frequently be saved by vigorous diabetic treatment plus incision and drainage without amputation. For example, a patient recovered from a very severe infection involving the whole left foot and ankle. On a diagnosis of gangrene the leg would certainly have been removed. However, in cases where there is massive dry gangrene from complete occlusion of the bloodvessels, the only possible curative treatment is amputation. Yet conservative treatment, even of the dry gangrenous areas, will often yield good results. Occasionally even the large black gangrenous areas on the feet are superficial and long-continued conservative treatment will eliminate the slough and preserve the leg.

The following case is given in more detail both because of the difficulty in diagnosing between intestinal obstruction in appendiceal peritonitis and the vomiting of the precomatose diabetic, and to illustrate a possible danger in the treatment of diabetes after operation.

CASE 9.—A female patient, aged 41 years, was admitted to the hospital after having had abdominal pain for 4 days. She was immediately operated upon and an acutely inflamed appendix removed. It was noted that there was considerable peritoneal exudate at the time of operation and a cigarette drain was inserted in the pelvis. Because of the danger of spreading the peritonitis the abdomen was not explored, although it was remarked that there was considerable distention. After operation sugar was found in the urine. She was not known to have had diabetes previously, although her father had died from diabetes.

For 3 days after operation she did fairly well. On the fourth day she began to vomit brownish liquid with an odor slightly suggestive of feces, became increasingly restless (not drowsy), the abdomen became still more distended and her temperature rose to 104° F. Her blood sugar was 320, urine sugar + + + +, acetone + and diacetic acid + +.

No liquids were permitted by mouth but a tube was inserted into the duodenum and about 2400 cc. of thin brownish fluid were drained out through the tube in 10 hours. During this time she was given 1000 cc. of 10 per cent glucose intravenously in divided doses. On the fourth day following operation she received 260 units of insulin in doses varying from 10 to 40 units each. The blood sugar dropped from 290 to 98, the patient was not quite so restless, did not complain of so much abdominal distress and the distention was somewhat less. The duodenal tube was removed and the patient encouraged to take liquid by mouth, which she did very freely, about 3000 cc., without apparent discomfort.

Following the use of the intravenous glucose the urine had contained sugar, 2+ to 4+ amounts, at the 2-hour examinations. At this time the blood sugar was 98, blood urea nitrogen 28 and blood CO₂ 48 volumes per cent. The patient said she was comfortable, but her skin was cold and clammy. About 7 hours later the patient suddenly went into collapse, the temperature rose again to 104°, the pulse to 120 and the skin felt cold and wet. She vomited a little brownish liquid and became quite restless, partially delirious. The duodenal tube was reinserted, against her strenuous vocal objections, although she was too weak to oppose it physically. In spite of draining off about 1 quart of brownish liquid, her condition progressed and she died, less than 45 minutes after protesting against the insertion of the tube.

Autopsy showed that the small bowel was greatly distended by liquid and occupied most of the abdominal cavity. There was slight dilatation of the stomach. There was a moderate degree of generalized peritonitis. About 8 inches proximal to the cecum was an S-shaped kink in the ileum caused by recent inflammatory adhesions which were apparently strong enough to obstruct the lumen, because the distal 8 inches of the ileum were of normal caliber and contained very little fluid. The large bowel was normal. The pancreas, liver, kidneys and spleen were normal to inspection and palpation. The urinary bladder contained about $\frac{1}{2}$ ounce of urine.

Discussion of Case 9. If the diagnosis of intestinal obstruction could have been made during the first 3 days and before the patient went into shock, the obstruction might have been relieved even at the expense of further spread of the peritonitis. Vomiting and abdominal pain are also symptoms of developing acidosis and coma, but severe acidosis was negated in this case by the almost normal blood CO₂ and very slight amount of acetone in the urine as well as by the restlessness and mental alertness of the patient (the opposite of coma drowsiness). After the patient survived the first shock and collapse large quantities of liquid were permitted by

mouth to further prevent the danger of acidosis. This large amount of liquid evidently hastened the end because the small intestines were greatly dilated postmortem. That she did not die in diabetic coma is shown by the absence of severe ketosis and the fact that up to within 45 minutes of her death she was restless and talked constantly. We believed that the moderate generalized peritonitis may have weakened the strength of the small intestinal muscular wall (a form of paralytic ileus) so that it could not force the intestinal contents past the relatively weak adhesions caused by a localized peritonitis of only a few days' standing.

Summary. An analysis of 312 consecutive cases of diabetes is presented. These patients were treated in an "open hospital" by 47 different physicians over a period of 8 years, with a total hospital mortality of 13.7 per cent. In the 59 surgical cases the mortality was 15.2 per cent and in the 253 medical cases there was a mortality of 13.5 per cent.

Although no difficulty whatever is experienced in the control of so-called "mild diabetes," under these conditions the utmost care and diligence is required for success with severe comatose or pre-comatose patients. The condition which calls most urgently for treatment in severe medical, as well as pre-operative and postoperative surgical cases, is the acidosis. Until the acidosis is successfully combated the height of the blood sugar and the glycosuria are of concern mainly as guides in the prevention of hypoglycemia from over dosage with insulin. After the acidosis has been controlled, the blood sugar can be finally standardized and the final traces of sugar removed from the urine by adjustment of diet and insulin.

ACUTE HEMORRHAGIC NECROSIS OF THE PANCREAS.

(A CLINICO-PATHOLOGIC STUDY WITH A NEW CLASSIFICATION
BASED ON ETIOLOGY.)

BY WILLIAM BRODY, M.D.,

RESIDENT PATHOLOGIST, PHILADELPHIA GENERAL HOSPITAL,

AND

R. P. CUSTER, M.D.,

CHIEF OF THE DIVISION OF PATHOLOGY, PHILADELPHIA GENERAL HOSPITAL, AND
ASSOCIATE IN RESEARCH PATHOLOGY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

(From the Division of Pathology of the Philadelphia General Hospital and the
Department of Pathology of the University of Pennsylvania.)

A SIMPLE classification of acute hemorrhagic necrosis of the pancreas is herewith presented, permitting etiology to determine the groups; it is believed that the pathogenesis in each group can

be established. The classification is based almost entirely upon observations made in our laboratory. It is not our intention to discuss the massive literature that has accumulated on this subject, except to mention that attention has been too strongly focused on the inflammatory group, the so-called "acute hemorrhagic pancreatitis" and that other groups, equally clear-cut, have been dismissed under such terms as "agonal or postmortem autodigestion."*

Pancreatic necrosis is not a disease entity; it is a reflection in the pancreas of disease process elsewhere. The nature of the reaction within the pancreas varies with the nature of the causative factor and presents a more or less characteristic gross and histopathologic picture; certain clinical features are sufficiently constant to bear out these etiologic and pathologic groups. Thus it is felt that the following classification of "acute hemorrhagic necrosis of the pancreas" is necessary:

I. Inflammatory.

(a) Dependent on infection and/or obstruction of the biliary tract.

(b) Dependent on infection from contiguous structures.

II. Degenerative.

(a) Dependent on cardiovascular disease.

1. Congestive heart failure type.

2. Hypertensive arteriosclerotic type (pancreatic apoplexy).

3. Embolic type.

(b) Dependent on general toxic phenomena.

(c) Dependent on trauma to the pancreas.

We have observed a large number of cases; of these, 30 were selected for detailed etiologic, clinical and pathologic analysis, and on this latter group the majority of the data recorded herein depends.

I. Inflammatory. (a) **DEPENDENT ON INFECTION AND/OR OBSTRUCTION OF THE BILIARY TRACT.** This, the least common of all, is the abdominal calamity recognized by the surgeon as "acute hemorrhagic pancreatitis." In the words of Moynihan, "the suddenness of its onset, the illimitable agony which accompanies it and the mortality attendant upon it, all render it the most formidable of catastrophes." Coming on usually after a good meal, excruciating epigastric pain occurs, frequently referred to the midback and loins; the patient goes rapidly into collapse, lividity of the face and sometimes patchy cyanosis over torso and extremities being notable. Exquisite abdominal tenderness is elicited, especially in the epigastrium, but rigidity is not in proportion. This is the type of case that at operation presents to the surgeon extensive fat necrosis, an acrid, serosanguinous, intraperitoneal exudate and a large, firm, edematous, red-black, friable pancreas lying at the bloody, semi-

* For complete consideration of the pathologic anatomy of the subject see Gruber; for the pancreas in heart disease see von Glahn and Chobot, Gerlei, and Schweizer.

destroyed base of the mesentery. This form has been in the past rather artificially divided into three types, *viz.*, hemorrhagic, gangrenous and suppurative, the difference, however, being only a matter of degree and duration, the essential nature identical. These cases almost uniformly give a history of previous recurring attacks of epigastric pain, nausea and vomiting of varying severity.

The etiologic agent is unquestionably a diseased biliary tract, as result of infection, small calculi or both. Many pathologists are disturbed on finding the bile passages entirely patent at necropsy examination and even the gall bladder free of stones. It is perfectly conceivable, however, that a small calculus, sufficient to cause temporary obstruction at the ampulla of Vater and reflux of infected bile into the main pancreatic duct, might be dislodged through vomiting and retching by the time the patient has reached the necropsy table.

A predisposing factor lies in the anatomic relation of the main and accessory pancreatic ducts, the variations of which have recently been described by Simkins. Moynihan feels that the two factors essential in the development of the condition are: (1) An anatomic arrangement of the parts at the termination of the two ducts which permits of their conversion into one channel by closure of the orifice of the ampulla into the duodenum, and (2) the presence of infected bile, associated or not with cholelithiasis in the gall bladder or in the bile ducts.

Reflux of duodenal contents into the pancreatic ducts is practically impossible. We attempted to produce this in the cadaver by ligating the duodenum below the ampulla, injecting colored substance into its lumen, and exerting extreme pressure. No coloring matter appeared within the pancreas, not even within the common bile duct. It has been said that an increase of intraduodenal pressure to 1000 mm. of water does not overcome the resistance of the ducts. Thus we believe that the anatomic arrangement and physical conditions existing in the body preclude this as an etiologic factor.

The cause of the actual necrosis is the presence of activated pancreatic juice within the substance of the gland. The activation of trypsinogen is accomplished normally by enterokinase of the duodenum, but we have shown that duodenal contents do not enter the pancreas. This activation, however, is accomplished by destructive bacterial action on the pancreatic cells, freeing the proteolytic enzymes therein. Pancreatic lipase needs an alkaline medium and bile for its activation. Since bile here enters the pancreas, as we believe, fat necrosis is a prominent feature of this group.

Pathologic Anatomy. The gross picture of the pancreas has already been mentioned. Histologically, evidences of the inflammatory character of this group are prominent; purulent exudate is seen in the ducts and often in the perilobular interstices. Wide-

spread necrosis of the parenchyma occurs, most prominent in the head and body, the tail being involved last. Hemorrhage is occasioned through necrosis of vessel walls by pancreatic ferments. Necrosis of fat is prominent in and about the gland. Late, no structure is recognizable; even the blood undergoes dissolution.

Of the other viscera the gall bladder and liver show the greatest variation from normal. The former organ is usually the seat of low-grade calculous cholecystitis and contains stones, more commonly of the fine, shot-like variety. The liver has, in many cases, undergone fatty metamorphosis and histologic examination shows the periportal region to be the seat of subacute to subchronic inflammation. Evidence of "shock," namely, extreme dilatation of capillary beds, is seen throughout the body.

(b) DEPENDENT ON INFECTION FROM CONTIGUOUS STRUCTURES. This is mentioned only to be dismissed in as many words, as it does not come within the scope of this paper. It usually follows suppurative peritonitis, portal thrombophlebitis, perirenal abscess (left) and like conditions in which any clinical manifestations emanating from the pancreas *per se* are masked by the symptoms of the major condition. Occasionally, however, chronic perforation of a peptic ulcer will seat itself in the pancreas, giving rise to a subacute pancreatitis which may present puzzling symptoms (such a case is mentioned by Gruber).

II. Degenerative. This second main class is divisible from the preceding one essentially by the difference in the gross and histologic picture of the pancreas, from the lack of evidence of an inflammatory process either in that gland or in the biliary tract and from striking differences in the clinical picture. The basic changes that we are considering are present, namely, necrosis and hemorrhage. Further subdivision of this group on etiologic grounds is made: (1) Those resulting from cardiovascular disease; (2) those associated with a general toxic process.

(a) DEPENDENT ON CARDIOVASCULAR DISEASE. 1. *Congestive Heart Failure Type*. The cardinal clinical features of cases in this subgroup are those of acute, congestive, right-sided heart failure in which upper abdominal complaints are prominent, especially epigastric pain, nausea and vomiting. The pain often radiates to one or the other hypochondriac regions and to the back, sometimes referred to the precordial region; pain in these cases is usually not severe and is accompanied by marked restlessness. Following the onset of these symptoms, the cardiac collapse becomes more prominent due to the concomitant acute myocardial degeneration, as will be seen later. These severe cases are usually accompanied by elevation of the blood sugar level (often ranging between 200 and 300 mg. per cent). Differentiation from the so-called "liver pain" may be difficult; failure to palpate an enlarged, tender liver and the presence of an elevated blood sugar level should be helpful. Rarely

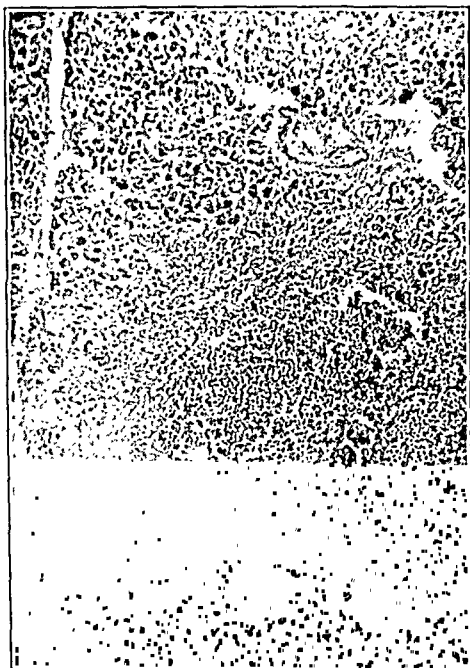


FIG. 1.—Inflammatory type (dependent on infection of the biliary tract). Suppurative focus in center; duct entirely destroyed. Necrosis is prominent; few acinar remnants persist. ($\times 90$.)



FIG. 2.—Inflammatory type (dependent on obstruction of the biliary tract). Extensive fat necrosis seen in center; reflux of bile prominent in this type case. ($\times 90$.)



FIG. 3.—Congestive heart failure type. Marked necrosis of pancreatic tissue; but few intact acini remain. Blood semidigested and not visible in photomicrograph. No fat necrosis. ($\times 82$.)



FIG. 4.—Recurrent congestive heart failure type. Majority of pancreatic tissue is necrotic, due to acute cardiac decompensation. In center is a V-shaped scar resulting from a similar previous attack from which the patient recovered. ($\times 82$.)

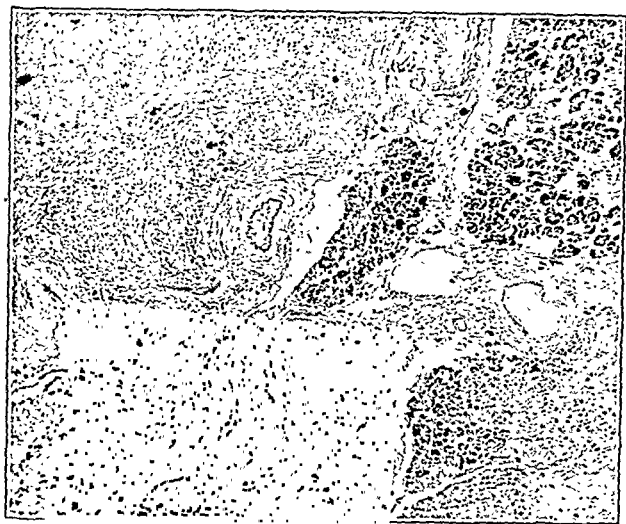


FIG. 5.—Hypertensive arteriosclerotic type. Five markedly sclerotic arteries seen in field, showing prominent internal elastic lamina. Pancreatic tissue preserved in upper right of field; remainder transformed into homogeneous, necrotic, hemorrhagic mass. No fat necrosis. No inflammatory reaction. ($\times 72$.)

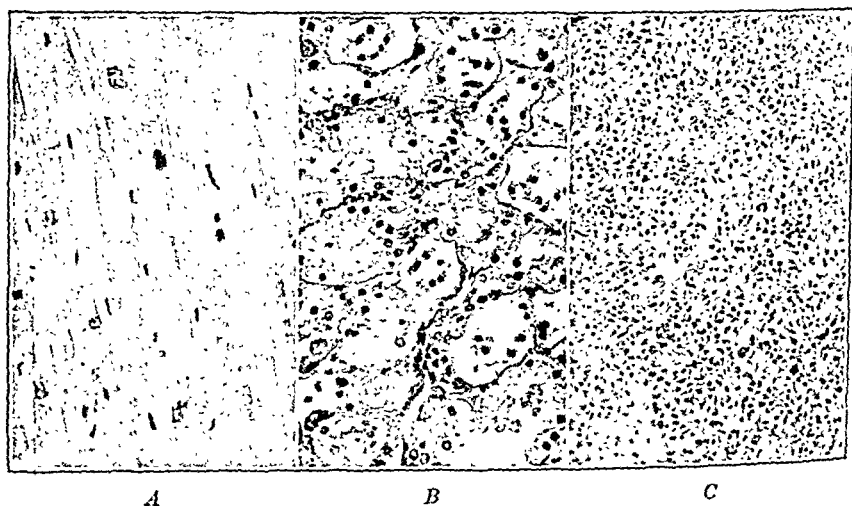


FIG. 6.—Degenerative type (dependent on general toxic phenomena). *A*, myocardium with extremely swollen and degenerated muscle fibers ($\times 350$). *B*, kidney with marked degeneration of tubular epithelium ($\times 350$). *C*, pancreas with extensive uniform necrosis of parenchyma ($\times 200$).

did we find an extensively engorged and tense liver at necropsy examination.

Directly related to the acuteness and severity of the cardiac decompensation, the pancreatic lesion may be mild or extensive. If mild, recovery occurs with reestablishment of circulatory compensation; we have mute evidence of this through the observation of fine to coarse, patchy fibrosis in the gland in cardiac cases with a history of repeated decompensation and with very little arteriosclerosis to account for scarring on that ground *per se*.

The pathogenesis of the pancreatic necrosis and hemorrhage in the congestive heart failure group appears to be clear-cut. Acute circulatory stasis in the organ leads to anoxemia in the tissue and increase in its hydrogen-ion concentration. This in turn disturbs the oxidized and reduced sulphydryl balance; in an attempt to supply oxygen to the already anoxemic tissue, oxidized sulphydryl becomes reduced, thereby augmenting the concentration of the latter, which acts as a catalytic agent for activation of trypsinogen in the acid medium (Waldschmidt-Leitz). In addition, in the autolysis of pancreatic cells, kinase is liberated, thereby furnishing a second activating catalyst (Morse). Lipase, being dependent both on an alkaline medium and on the presence of bile for its activation, is inert under the conditions existing here; hence, fat necrosis is not a feature of this group. A second factor, not so well established, however, is the increase in permeability of the upper intestinal mucosa due to its extreme congestion and degeneration, thus promoting the rate and decreasing the selectivity of absorption through this mucous surface; absorption of toxic products from the upper bowel may occur and enhance the acute degenerative changes seen in all of the viscera.

Pathologic Anatomy. Grossly the pancreas is always markedly congested, presenting a purplish-red color; the consistency is soft, either uniformly throughout or present in localized areas most frequent in the body. Punctate hemorrhages are often seen on the surface. The sectioned surface shows the areas of softness appearing as ill-defined, almost semifluid patches in which free hemorrhage is prominent. In those instances in which the degenerative process has occurred uniformly throughout, the organ is mushy and does not maintain its form; petechial hemorrhages are scattered diffusely.

Microscopic examination in the first instance shows focal areas of parenchymal necrosis lying in pancreatic tissue that is either normal or only moderately degenerated. In the latter type necrosis is almost uniform throughout; some areas, however, are degenerated to a less degree. Hemorrhage is not as evident microscopically as macroscopically, the blood cells sharing the fate of the parenchymal elements; this is more especially true in the severe instances. (The question of postmortem autolysis has arisen in this connection;

Recent	Pathologic anatomy				Histopathology			
	Cerebral	Terminal psychotic delirium (1 case)	Dependent on primary structure involved. No generalization can be made	Stupor	Occasional hemiplegia	Stupor. Loss of sphincteric control. (Concomitant with meningitis, tetanus or pneumonia—1 case each)		
Pancreas		Large, firm, friable, patchy red-black, with fat necrosis in pancreatic bed and mesentery. Hemorrhage at mesenteric base. Bloody, acid peritoneal fluid	Suppurative pancreatitis with focal softening	Normal size; focal or diffuse softening; cyanotic, with focal or diffuse hemorrhage. No fat necrosis. No peritoneal exudative reaction	Normal size; focal to massive diffuse hemorrhage (intra- or peripancreatic) with focal or diffuse necrotic softening. Gross arteriosclerosis notable. No peritoneal fluid, no fat necrosis	Normal size; uniformly soft and mushy; dark purplish-red, with scattered hemorrhages; slight perilymph nodal fat necrosis in mesentery; no peritoneal fluid		
Liver		Large (av. wt. 2500 gm.); soft and yellow	Negative	Congestion. Mild degeneration	Congestion. Occasional cirrhosis	No characteristic changes		
Gall bladder and ducts		Chronic cholecystitis; many small, shot-like calculi (2 cases). Ducts patent (3 cases)	Negative	Usually negative. Occasional large calculus	Negative	Negative		
Heart		Av. wt. 373 gm.; no constant lesion; av. blood pressure—100/70 (1 case), not obtainable (2 cases)	Negative	Av. wt. 525 gm.; soft, flabby, dilated; occasional chronic valvular lesion; occasional coronary disease (non-occlusive); av. blood pressure 147/78	Av. wt. 542 gm.; firm, concentric hypertrophy; coronary sclerosis; no occlusion; av. blood pressure 237/110	Av. wt. 340 gm.; extremely soft and flabby; no other notable lesions; av. blood pressure 129/63		
Arterial tree		Negative	Negative	Slight to moderate sclerosis	Marked generalized sclerosis; mesarteritis degenerative (1 case)	Negative		
Other viscera		Show the extreme capillary congestion of "shock," esp. lung and kidney	Depend on primary lesion	Congestive phenomena; mild degenerative changes	Congestion and hemorrhage; arteriosclerosis	Marked toxic nephrosis		
Pancreas		Purulent exudate in and/or about ducts (visible where necrosis is incomplete); extreme irregular necrosis of parenchyma and fat; interstitial hemorrhage; (pancreas usually the seat of fatty infiltration)	Suppurative peri- or interlobular pancreatitis with little involvement of parenchyma early	Focal or diffuse necrosis; congestion and scattered hemorrhage; scarring in recurrent cases; no fat necrosis; no inflammation	Hemorrhage, necrosis and extreme arterio-arteriosclerosis (occasional occlusion and visible rupture); no fat necrosis; no inflammation	Fairly uniform necrosis with scattered, partly digested hemorrhage; occasional slight fat necrosis; no inflammation		
Liver		Subacute to subchronic periportal hepatitis, marked fatty metamorphosis	Negative	Acute and chronic passive congestion; no periportal hepatitis	Acute passive congestion; proliferative periportal hepatitis with cirrhosis (3 cases)	Parenchymatous degeneration; acute passive congestion		
Other viscera		Extreme congestion	Depend on primary lesion	Marked myocardial degeneration	Coronary sclerosis, myocardial degeneration	Marked myocardial degeneration; necrotic nephrosis		

Chiari felt that necrosis seen in our degenerative classes was agonal or postmortem "Autodigestionsnekrose," to this Gruber agrees. In our laboratory the bodies are handled uniformly and refrigerated promptly after death; we have examined the pancreas 3 to 6 days postmortem and have found that organ well preserved. Gruber notes in this type of case a diffusion of iron throughout the tissue, demonstrable by the Turnbull blue reaction, yet classes the necrosis agonal or postmortem; we feel that this observation would suggest strongly the congestive origin of the necrosis). The other viscera, especially the heart and kidneys, to a lesser extent the liver, show a rather marked degree of acute degeneration, rather more than would be expected as a result of the congestive phenomena alone. The gall bladder and bile ducts (both intrahepatic and extrahepatic) show little or no evidence of infection. Occasionally calculi may be found in the gall bladder, but they are usually of larger size, not capable of traversing the duct.

2. *Hypertensive Arteriosclerotic Type.* The occurrence of sudden, severe, epigastric pain in a hypertensive individual should suggest so-called pancreatic apoplexy, sometimes associated with cerebral apoplexy and occasionally with the dissecting aneurysm of "mesarteritis degenerativa sine syphilis" (one of our cases showed this latter condition, with dissection along the branches of the celiac axis). Phenomena of cardiac decompensation are not prominent in this type of case, but usually appear if the lesion is severe and the case terminates fatally. These cases, as well, may present minor lesions that heal with residual scarring of the organ, but are differentiated histologically from the congestive type by the prominence of vascular sclerosis or arteritis in the pancreas and other organs.

The hemorrhage and concomitant local necrosis in the pancreas are the result of a ruptured vessel; this may be due simply to the combination of hypertension and diseased vessels poorly supported in the loose parenchyma of the organ, or it may be initiated by the excessive vomiting of the gastrointestinal crises or of the uremia so characteristic of arterionephrosclerosis with renal failure.

Pathologic Anatomy. The pancreas is usually not enlarged; the apoplectic lesion is often not visible until the cut surface is examined, although the local area of softening may be palpable. Sometimes, however, the head lies in a massive peripancreatic hemorrhage. The lesion is more often single and situated in the head; less often is the hemorrhage massive within the organ, spreading along the interstices with extreme destruction of the parenchyma. Histologically, vascular sclerosis, senile or arteritic, is the striking feature; occasionally one is fortunate enough to observe actual breaks in the arteries and veins. Hemorrhage occupies the foreground of the picture and necrosis is less prominent than in the preceding group (thus, hemorrhage alone is not the prime factor in the cause of necrosis, as other conditions mentioned above are

necessary therefore). Necrosis under these circumstances is primarily a pressure necrosis; secondarily, anutritional; finally, to a lesser extent, enzymal.

The other viscera in these apoplectic cases do not show degenerative changes unless from some extraneous factor. Vascular disease of other organs, however, is usually striking. Here again, disease of the biliary tract is not a feature.

In none of our cases was pancreatic apoplexy associated with coronary occlusion, although the clinical features in some instances suggested that that phenomenon has occurred; some reached the necropsy table with the diagnosis of coronary occlusion, some with the diagnosis of mesenteric thrombosis. These latter two vascular accidents tax the diagnostic acumen.

3. *Embolic Type.* We have had no experience with this group. It is almost invariably associated with subacute bacterial endocarditis, the pancreas sharing to a lesser extent the embolic accidents of other viscera. (Hematogenous pancreatitis should receive mention, although it is rather rare; it is a question whether to class it with this group or with the inflammatory group, depending on whether one considers it due to minute bacterial emboli.) For a complete study of infarctive phenomena in the pancreas in heart disease reference is made to the article of Gerlei.

(b) **DEPENDENT ON GENERAL TOXIC PHENOMENA.** This group is identified positively only at necropsy examination by the presence of an extremely necrotic pancreas in association with an almost equally marked necrosis of the other viscera, in the absence of cardiac or vascular lesions, due to an ingested or unknown toxin. Most of the cases in our series were associated with some intracranial disease (acute alcoholic psychosis, pneumococcus meningitis, epilepsy, paresis, thrombosis, etc.) that we believe, for the most part, is either concomitant (and dependent on the same etiologic agent) or merely coincidental.

Persistent nausea and vomiting appeared to be the most common subjective symptom of this group, sometimes associated with intense upper abdominal pain (the latter was not elicited in some instances on account of stupor). In many cases gastrointestinal symptoms were attributed by the clinician to the associated intracranial phenomena, some to intestinal obstruction or ruptured viscus. Almost uniformly, blood sugar was markedly increased. Uniformly the patients went into collapse and died.

Pathologic Anatomy. The pancreas is extremely soft and necrotic throughout; hemorrhage is not prominent, although the organ is a dusky red color. Histologically the architecture is lost, only shadows of acini are visible; not the slightest evidence of acute inflammation is seen. Very slight fat necrosis may be present in the periphery of the gland. (Two cases showed fat necrosis surrounding lymph nodes in the mesentery; this was attributed to

retrograde lymph flow from the pancreas carrying lipase with it.) Other viscera suffer in proportion; the heart invariably shows an extremely extensive acute myocardial degeneration; invariably the kidneys are the seat of necrotic nephrosis. The liver cords are converted into an almost anuclear, homogeneous mass; some cases show a lesser degree of damage where death occurs rapidly. The gastrointestinal tract suffers markedly in this type of case; the stomach is dilated and filled with regurgitated bile and the mucosa of the stomach and intestines is exceedingly congested and often necrotic, sometimes showing histologically an inflammatory reaction in the submucosa.

(c) DEPENDENT ON TRAUMA TO THE PANCREAS. Opie has stated: "Hemorrhagic and gangrenous pancreatitis with disseminated fat necrosis has in a few instances so directly followed abdominal injury that the relation to traumatism cannot be doubted. Injury to the pancreas is usually associated with such severe damage to adjacent structures that a fatal result is rarely referable to the gland. Incisions into the pancreas of animals heal readily." It has been shown experimentally that obstruction to the circulation associated with injury to the parenchyma may be followed by hemorrhagic necrosis of the pancreas; this suggests that traumatic thrombosis of blood-vessels may play a part in the pathogenesis.

Comment. Rational treatment of acute hemorrhagic necrosis of the pancreas depends entirely upon a clear conception of its etiology and of the various forms in which it may exist. In the inflammatory type prompt, intelligent surgical intervention is imperative; in all other instances surgery seems to be definitely contraindicated. Those cases associated with congestive heart failure require heroic therapy directed toward restoring circulatory compensation; the hypertensive group calls for measures directed toward the underlying cause. For the toxic cases little can be done unless the noxious agent can be identified and eliminated.

During a discussion of so-called "acute hemorrhagic pancreatitis" recently, a surgeon mentioned the fact that he had of late become more conservative in advising operation in certain cases, having observed recovery in instances without surgical intervention. We believe that these latter were cases that fall in our degenerative group and that the surgeon had unconsciously come to recognize it without knowledge of the underlying features. How many surgeons, examining a patient with severe upper abdominal pain, nausea, vomiting and sometimes collapse, would advise against exploratory laparotomy? Fortunately modern surgery is moving slowly toward a policy of conservatism.

If the patient is viewed through a wide-angle lens rather than through one of short focal length (and that focus centered between the umbilicus and xyphoid) fewer patients will be subjected to and their death hastened by unnecessary operation.

Summary. A simple classification of acute hemorrhagic necrosis of the pancreas has been evolved in which etiology, pathologic anatomy and clinical manifestations are closely bound, as follows:

I. INFLAMMATORY.

(a) Dependent on infection and/or obstruction of the biliary tract

(b) Dependent on infection of contiguous structures.

II. DEGENERATIVE.

(a) Dependent on cardiovascular disease.

1. Congestive heart failure type.

2. Hypertensive arteriosclerotic type.

3. Embolic type.

(b) Dependent on general toxic phenomena.

(c) Dependent on trauma to the pancreas.

The relation of this classification to treatment has been discussed.

BIBLIOGRAPHY.

- Chiari, H.: *Prag. med. Wehnschr.*, 1900, **25**, No. 14.
 Gerlei, F.: *Virch. Arch. f. path. Anat.*, 1930, **276**, 148.
 Gruber, G. B.: *Henke-Lubarsch Handb. d. spez. path. Anat. u. Histol.*, 1929, **2**, 457.
 Morse, W.: *Applied Biochemistry*, Philadelphia, W. B. Saunders Company, 1925, p. 459.
 Moynihan, B.: *Abdominal Operations*, 4th ed., Philadelphia, W. B. Saunders Company, 1926, **2**, 454.
 Opie, E. L.: *Osler's Modern Medicine*, Philadelphia, Lea & Febiger, 1926, **3**, 672.
 Schweizer, R.: *Virch. Arch. f. path. Anat.*, 1930-31, **279**, 780.
 Simkins, S.: *Am. J. Med. Sci.*, 1931, **182**, 626.
 Von Glahn, W. C., and Chobot, R.: *Am. J. Path.*, 1925, **1**, 373.
 Waldschmidt-Leitz, E.: *Lecture, Univ. of Penna.*, April 22, 1932.

THE ABSENCE OF OSTEOPOROSIS DEMONSTRATED CHEMICALLY IN CLINICAL HYPERTHYROIDISM.*

BY ARNOLD E. OSTERBERG, B.S., M.S., PH.D.,

ASSOCIATE IN SECTION ON CHEMISTRY, THE MAYO CLINIC; ASSISTANT PROFESSOR OF
 PHYSIOLOGIC CHEMISTRY, THE MAYO FOUNDATION FOR MEDICAL EDUCATION
 AND RESEARCH, GRADUATE SCHOOL, UNIVERSITY OF
 MINNESOTA, ROCHESTER, MINN.,

AND

RALPH G. MILLS, B.A., M.D.,

WILEY-SMITH CLINIC, FOND DU LAC, WIS.; FORMERLY OF THE SECTION ON PATHOLOGIC
 ANATOMY, THE MAYO CLINIC.

THE work of Aub and his coworkers, in 1926, in investigating the influence of the thyroid gland on the metabolism of calcium showed that patients whose diets were deficient in calcium but were adequate in other respects had a negative calcium balance. Patients

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TABLE 1.—PARTIAL SUMMARY OF DATA EXPRESSED IN AVERAGES.

Age group.	Number of controls, with sex.	Percentage of ash in dry bone.				Percentage of calcium in ash.				Percentage of phosphorus in ash.				Calcium to phosphorus ratio.			
		Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.		Control.		Patient with hyperthyroidism.	
		Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
15-20 . . .	3 F																
	Rib																
	Pelvis	57.4	55.3	50.8	51.9	37.73	38.26	37.55	36.90	17.36	18.19	17.31	17.31	2.17	2.11		2.13
22-23 . . .	2 F																
	Rib																
	Pelvis	58.0	51.5	56.2	54.1	38.46	39.06	37.60	37.30	18.30	18.87	17.81	16.90	2.10	2.19	2.11	2.20
30-33 . . .	1 F																
	Rib																
	Pelvis	58.9	54.9	56.1	48.6	37.52	37.59	40.17	39.40	17.57	17.48	19.28	17.12	2.14	2.15	2.08	2.30
34-37 . . .	3 F																
	Rib	60.1	51.8	50.4	52.2	38.81	37.28	37.40	36.82	17.60	17.92	16.51	17.05	2.13	2.09	2.26	2.00
37-38 . . .	2 F																
	Rib	53.9	52.1	51.6	48.4	37.53	39.17	39.80	38.40	17.15	18.20	18.18	18.20	2.16	2.15	2.19	2.10
37-42 . . .	5 F																
	Rib	58.0	53.2	57.8	50.5	37.30	37.81	34.83	36.78	17.74	17.81	18.38	18.33	2.09	2.13	1.90	2.00
40-46 . . .	3 F 5 M																
	Rib	53.5	54.3	49.4	55.5	38.43	38.97	37.70	37.10	18.43	18.11	18.90	18.70	2.06	2.11	1.99	1.99
	Pelvis	52.4	52.3	55.5	57.8	37.38	37.08	37.10	37.08	18.06	17.63	18.70	18.70	2.03	2.07	1.99	1.99
46-50 . . .	1 F 5 M																
	Rib	51.3	56.4	57.8	51.8	36.59	39.05	36.80	36.85	17.23	17.75	14.71	17.78	2.19	2.19	2.50	2.07
	Pelvis	51.1	55.1	57.3	57.8	37.87	37.52	37.37	37.38	17.41	17.55	17.32	17.78	2.16	2.14	2.12	2.10
50-53 . . .	1 F 5 M																
	Rib	51.5	55.6	50.6	51.2	40.38	36.31	38.70	37.40	19.20	17.78	18.39	18.18	2.13	2.03	2.10	2.07
	Pelvis	56.5	51.3	51.4	51.6	37.55	38.77	37.32	39.42	17.66	18.10	18.67	17.47	2.12	2.14	2.00	2.26
55-58 . . .	5 F 4 M																
	Rib	49.5	49.9	47.8	52.2	38.03	40.56	37.25	35.10	17.14	18.01	17.20	16.87	2.25	1.96	2.16	2.08
	Pelvis	49.3	51.6	51.4	49.4	37.82	37.53	37.60	36.35	17.93	17.51	16.89	17.86	2.11	2.14	2.22	2.01
60-62 . . .	2 F 6 M																
	Rib	45.9	41.7	45.2	44.4	37.77	40.11	37.90	38.60	17.70	18.06	17.10	18.75	2.10	2.15	2.22	2.06
	Pelvis	40.2	42.8	37.3	42.4	38.08	37.30	41.20	37.20	17.75	17.74	19.21	18.69	2.12	2.08	2.12	1.99
63-65 . . .	2 F 2 M																
	Rib	42.4	50.4	40.7	35.2	38.50	37.29	38.21	36.10	17.70	18.80	18.42	18.45	2.19	2.09	2.07	1.96
	Pelvis	35.3	53.9	36.0	36.0	38.33	36.20	38.74	38.74	17.85	18.27	18.42	18.45	2.13	2.05	2.07	1.96
66-68 . . .	3 M																
	Rib	53.9	49.2	40.6	51.4	37.35		33.17	37.80	17.71	17.27	17.02	17.02	2.11	2.14	2.18	1.95
70-75 . . .	2 F 0 M																
	Rib	42.2	44.3	41.9	40.2	37.45	37.61	37.69	37.69	17.78	18.50	17.86	17.86	2.10	2.15	2.11	2.08
	Pelvis	45.6	44.8	40.2	40.2	37.25	37.85	37.36	37.36	17.92	17.91	17.90	17.90	2.07	2.08	2.08	2.08
Final averages . . .																	
	Rib	49.1	53.0	47.3	51.9	38.16	38.17	37.76	37.09	17.87	17.82	17.28	17.28	2.15	2.11	2.19	2.06
	Pelvis	48.2	52.3	40.3	50.2	37.66	37.80	38.27	37.73	17.73	17.86	17.96	17.96	2.11	2.12	2.12	2.12

with either exophthalmic goiter or adenomatous goiter with hyperthyroidism, as well as normal persons whose metabolism had been elevated by administration of thyroxin or thyroid extract, excreted considerably more calcium than the control subjects. In the instance of one patient with exophthalmic goiter, whose basal metabolic rate was high, the output of calcium was increased approximately fivefold. Excretion of phosphorus behaved similarly, but to a lesser degree. These experiments tended to indicate that the excreted calcium was of endogenous origin, and that its probable source was the bones. This possibility was offered by Aub and his coworkers in their roentgenologic studies, and has been demonstrated, also, by Plummer and Dunlap and by Dunlap and Moore, who have observed decreased density of the bones of patients with exophthalmic goiter. Osteoporosis was found to affect the entire osseous system, especially the spongy bones and those with superficial coverings, such as the skull, ribs and bones of the extremities. In the extremities it was more noticeable in the epiphysis and ends of the diaphysis than elsewhere. The loss of calcium varied in degree from that producing only a slight increase in translucence, so trivial as to escape casual notice, to marked and unquestionable rarefaction. Slight changes became apparent by photographing the hand of the patient on the same plate, or by the same technique, as that of a normal person. When absorption of calcium was more pronounced, the shadow cast by the bone was faint, the trabeculae were not very distinct and the bone appeared structureless. The change was more diffuse than localized, and if it was localized it called for differential diagnosis from atrophy, malignancy, infection, etc. The view was expressed that the degree of decalcification was in direct relation to the severity and duration of the hyperthyroidism, and that decalcification was usual rather than unusual. Aub, Bauer, Heath and Ropes elaborated the previous work, but reached the same conclusions with reference to the effect of hyperthyroidism, on structure of bone, and elimination of calcium. In some instances loss of calcium was greatly in excess of the increase in basal metabolic rate.

The possible criticism which might be offered in drawing definite conclusions from the roentgenologic studies would be in the selection of the controls, since it is well known that the degree of activity, occupation and other factors, as well as age and sex, influence density of bone.

It has been found that administration of iodine, and partial removal of the thyroid gland or of the toxic adenoma, tend to cause return of the calcium balance toward normal. Aub, Bauer, Heath and Ropes stated: "It is not to be expected that all cases of hyperthyroidism would show osteoporosis of the bones because of this increased calcium elimination, which could probably be compensated for by a diet containing an adequate amount of

calcium. In some cases of long duration, however, this increased calcium loss from the bones may be apparent in Roentgen ray pictures." They concluded that the change in the bones was attributable to withdrawal of calcium phosphate, although they admitted the possibility that some of the calcium might be in the form of calcium carbonate. The ratio of calcium to phosphate indicated that tricalcium phosphate was the form in which most of the mineral matter was lost. The elevation of the basal metabolic rate was not in itself the cause of the loss of mineral.

With this work as a background, it occurred to the authors that if such gross differences were present in the bones of persons with hyperthyroidism as to be demonstrable by roentgenogram, it might be possible to demonstrate directly that the increased amount of calcium and phosphorus excreted could be shown to be derived from bones by analysis of bones removed from patients who had died and who had presented a history of hyperthyroidism. Also, data thus secured would demonstrate whether the decrease in density was due to loss of calcium and phosphorus as tricalcium phosphate, with a resultant high percentage of calcium carbonate remaining, or whether decreased density exists because of porosity due to the presence of an increased amount of organic matter. Naturally, many factors were involved in the selection of such cases, and it was apparent at the outset that much negative evidence might be accumulated. Factors such as duration of the disease, whether operation had been submitted to, the length of time since operation, the basal metabolic rate, etc., offered complications in drawing conclusions from the analytic data obtained by analysis of the bones. However, it was deemed advisable to proceed to obtain these data, with the hope that the results could be correlated with the clinical history, and that positive evidence could be obtained by association between the osteoporosis of hyperthyroidism as observed clinically and the disease as a whole.

Methods. Two samples were removed in each case, one from the right fifth rib, adjacent to the place where it would be severed at necropsy (performed as a routine) and the other from the left superior ramus of the pubic bone. The former was believed to reflect bony changes most readily, whereas the latter was assumed to be the least affected of any portion of the available bony system. The data which it was deemed advisable to secure included specific gravity, content of moisture, total solids, mineral matter, organic matter, content of calcium, content of phosphorus and the calcium to phosphorus ratio. Determinations of magnesium also were made, but the results seemed to be of no significance.

Because of the infrequency with which patients who present recent histories of hyperthyroidism come to postmortem examination, collection of material extended over 3 years, necessitating that the samples of bone be placed in 95 per cent alcohol for temporary

storage. This solution was found to be superior to formaldehyd because the periosteum could be more readily removed in cleaning the final samples for examination. This mode of preservation tended to remove some of the water content of the bone, but the defect was partially remedied by leaving the bone in water for a day before weighing or measuring its volume. This procedure probably did not accurately restore the bone to its original condition, but the advantages outweighed the disadvantages, and the results of the various determinations are at least comparable.

However, in evaluating the final data it seemed advisable to consider only those data based on the dry bone material, for the content of moisture and determinations of specific gravity, although interesting in themselves, offer no solution to the problem. Determinations of moisture were made by drying at 110° C. Specific gravity was determined from the weight and the volume as measured by displacement of a column of water in a graduated buret.

The samples taken from the ribs were uniform in character; care was taken to eliminate as far as possible variations in weight, such as would occur if the ends of the fragments were not uniformly cut across. One would, therefore, expect comparable and reliable results from this source. The ramus of the pubis, on the other hand, was subject to considerable variation in the size and shape of the fragment secured. Effort was made to preserve the most dense portion of the bone, but variation occurred in spite of every precaution. In evaluation of the results account must be taken of this variability.

The dry weight of the sample was determined by differential weighing in crucibles, following which it was incinerated in an electric furnace. The loss of weight represented organic matter; the residual weight was ash.

To determine the mineral content, the ash was dissolved in hydrochloric acid, made up to a volume of 100 cc., and the resulting solution was set aside for chemical examination. Aliquot parts of this solution were taken for determination of calcium and phosphorus. Determinations of calcium were made on portions of 3 cc., according to the procedure of Kramer and Howland, and determinations of phosphorus were made on portions of 1 cc., according to the procedure of Bell and Doisy.

Table 1 is a condensation of the more essential analytic data obtained. The values for specific gravity and content of moisture have been omitted, because correlation between the results of analysis of control specimens and of specimens from patients with hyperthyroidism seemed impossible. Study of the statistical data warranted its presentation by averages. Consequently, in the various age groups the average values are given. No constant difference is apparent in either the percentage of ash, percentage of calcium or phosphorus or the calcium to phosphorus ratio. However, as

seen from the general average, there is a tendency to higher mineral content in the control cases than in the cases of hyperthyroidism. This increase in ash is not of sufficient magnitude to be obvious in roentgenograms. The calcium to phosphorus ratio is slightly greater than 2. In some cases of hyperthyroidism the calcium to phosphorus ratio is greater than that of the controls, but this is not constant, and no particular significance can be attached to it. That the value is not 1.93, as in dry bone or apatite, is due to the fact that the results were obtained on incinerated material from which carbon dioxide was lost. If constant, marked osteoporosis existed, one would expect a calcium to phosphorus ratio considerably greater than 2. This was obtained in 1 control case, in which the calcium to phosphorus ratio was 2.62. The subject presented clinical osteoporosis, but no hyperthyroidism. One other instance of a high calcium to phosphorus ratio was found in a case of hyperthyroidism. The bone from the rib, in this case, had a calcium to phosphorus ratio of 2.5, whereas the ratio in the pubic bone was normal.

TABLE 2.—SUMMARY OF DATA CONCERNING PATIENTS WITH HYPERTHYROIDISM FROM WHOM SPECIMENS OF BONE WERE SECURED.

Case No.	Age, years, and sex.	Type of hyperthyroidism.	Duration of disease.	Type of thyroidectomy and weight of removed tissue in grams.	Time of death after operation.	Basal metabolic rate.
1	18 F	Exoph. goiter	8 months	Subtotal; 267	2 days	+108
2	22 F	Exoph. goiter	3 years	No operation	No oper.	+80
3	32 F	Rec. exoph. goiter	3.5 years	Subtotal; 8	6 months	+57
4	34 F	Goiter*	Unknown	Unknown	1 year	
5	36 F	Exoph. goiter	6 months	Partial; 20	1.5 months	+40
6	40 F	Exoph. goiter	3 months†	Subtotal; 86	4 days	+31
7	46 F	Exoph. goiter	9 months	Subtotal; 50	16 days	+83
8	48 M	Exoph. goiter	2 months	Subtotal; 12	9 days	+45
9	48 F	Exoph. goiter	4 months	Resection of rt. lobe; 62	15 hours	+57 +64
10	53 M	Exoph. goiter	18 months	No operation	No oper.	+41
11	53 M	Exoph. goiter	4 months	Subtotal; 54	2 days	+47
12	53 F	Exoph. goiter	3 months	No operation	No oper.	+49
13	57 F	Exoph. goiter	1 year	Subtotal; 100	2 days	+60
14	58 M	Toxic adenoma	7 years	Unknown; operation elsewhere	5 years	
15	58 F	Toxic adenoma	1 year	Subtotal; 70	2.5 years	+10
16	60 M	Toxic adenoma	4 months	Subtotal; 35	19 months	+51
17	63 F	Toxic adenoma	3 months	No operation	No oper.	
18	65 F	Hypertr. adenoma	2 years	Subtotal; 47	3 days	+71
19	66 M	Exoph. goiter	8 months	Subtotal; 56	3 days	+64
20	68 F	Adenoma	4 months	Subtotal; 32	4 years	+17
21	70 M	Hyperthy.	2 years	Subtotal; 126	8 days	+38
22	71 M	Toxic adenoma	Unknown	No operation	No oper.	+20
23	72 M	Exoph. goiter	2 years	Subtotal	2 days	+29

* Type unknown, removed elsewhere 1 year before.

† Goiter present 22 years.

Table 2 is presented to show variable factors that may exist in cases of hyperthyroidism, which may lead to variable factors in structure of bone. For example, the time of death after operation varied from 15 hours to 5 years; the duration of the disease, as

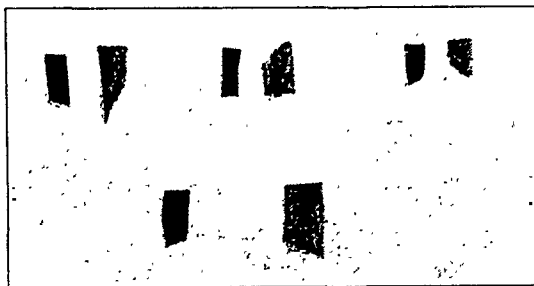


FIG. 1.—The specimens are of pubic bone (more dense) and of rib (less dense). The pair of specimens, below, was obtained from the patient represented in Case 1 (Table 2). The three pairs of control specimens, above, also are of pubic bone and of rib, and were obtained from subjects of the same sex and age group, but who did not have hyperthyroidism.

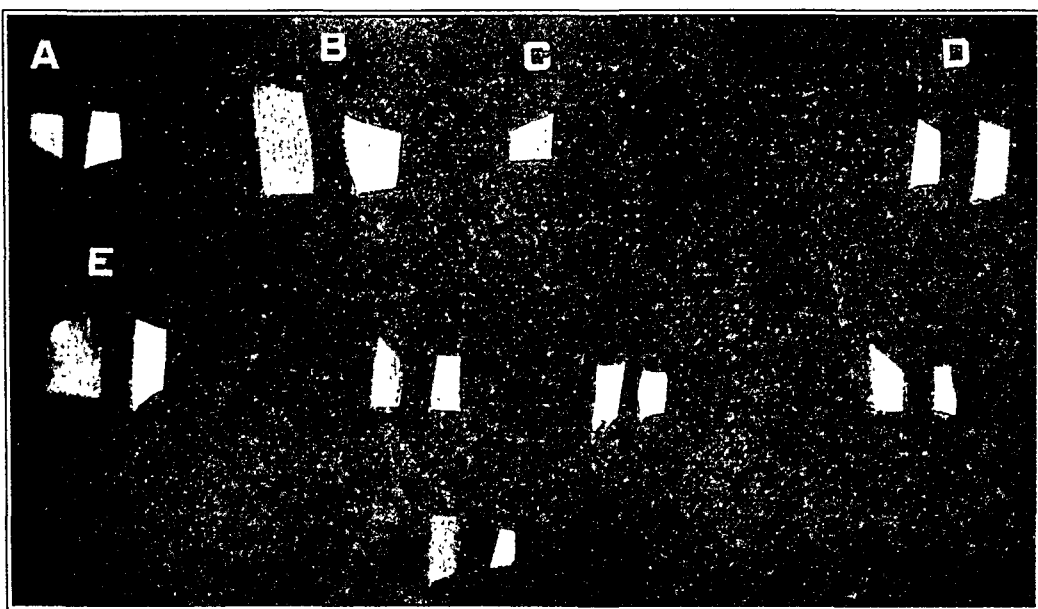


FIG. 2.—The specimens are similar to those in Fig. 1. The pair of specimens, below, was obtained from the patient represented in Case 7 (Table 2); the other specimens are controls, obtained from subjects of the same age group, but who did not have hyperthyroidism. Control specimens A, B, C, D and E were obtained from males, the unlettered control specimens from females. Specimen C is of rib.

elicited from the history, varied from 2 months to 7 years, and the basal metabolic rate from +10 to +108. Obviously, some of these persons would be more likely to present clinical osteoporosis than others, and one would expect that those patients who presented histories of moderately increased metabolism for a period of several

months, and whose death followed very soon after partial thyroidectomy, precluding any possibility of regeneration of bone, would show by roentgenologic examination decreased opacity of the bone. Roentgenograms of specimens in 4 such cases (Nos. 1, 17, 18 and 19, Table 2) are shown in Figs. 1, 2 and 3. They represent in Table 1, respectively, the age groups 15 to 20 years, 40 to 46 years, 63 to 65 years and 66 to 68 years. These pictures demonstrate no apparent difference in opacity between the specimens from patients with hyperthyroidism and the controls. Table 1 also does not disclose striking variations in content of ash or in calcium to phosphorus ratio. Case 4, however, is a case of osteoporosis in which the calcium to phosphorus ratio was found to be 2.62.

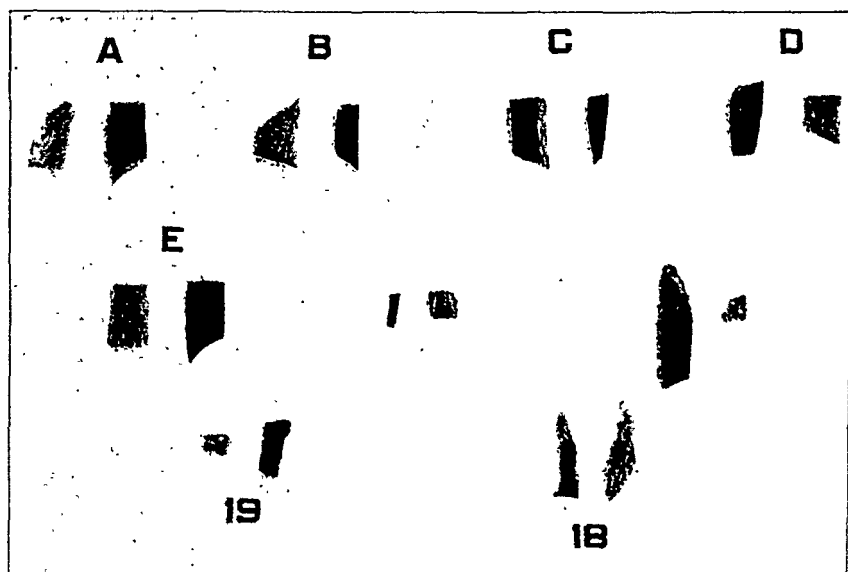


FIG. 3.—The specimens numbered 18 and 19 were obtained, respectively, from the patients represented in Cases 18 and 19 (Table 2). The general plan is the same as that of Figs. 1 and 2. Control specimens, obtained from subjects of the same age group, but who did not have hyperthyroidism are represented. Specimens A, B, C, D and E were obtained from males and are to be compared with specimen 19. The unlettered control specimens were obtained from females and are to be compared with specimen 18.

Summary. It has been shown previously that hyperthyroidism may produce excretion of endogenous calcium, which may result in osteoporosis demonstrable by roentgenogram.

In this study, chemical and roentgenographic study of bone, removed postmortem from 23 patients who had had histories of hyperthyroidism, and from 78 control subjects, failed to demonstrate a sufficiently constant difference in percentage of ash, percentage of calcium, calcium to phosphorus ratio or roentgenographic opacity

to warrant a conclusion that hyperthyroidism is always accompanied by some degree of osteoporosis.

Failure to demonstrate a difference may be explained by assuming that there was compensatory ingestion of calcium, or other variable factors that may occur in clinical hyperthyroidism. Obviously, ingestion of calcium is not controlled in clinical hyperthyroidism as it may be controlled in experimental hyperthyroidism. Further work of this nature in clinical hyperthyroidism seems unnecessary, since the results apparently can be only inconclusive.

BIBLIOGRAPHY.

1. Aub, J. C., Bauer, W., Heath, C., and Ropes, M.: Studies of Calcium and Phosphorus Metabolism. III. The Effects of the Thyroid Hormone and Thyroid Disease, *J. Clin. Invest.*, 1929, 7, 97.
2. Bell, R. D., and Doisy, E. A.: Rapid Colorimetric Methods for the Determination of Phosphorus in Urine and Blood, *J. Biol. Chem.*, 1920, 44, 55.
3. Dunlap, H. F., and Moore, A. B.: Osteoporosis Secondary to Hyperthyroidism, *Med. Clin. North America*, 1929, 12, 1511.
4. Heath, C. W., Bauer, W., and Aub, J. C.: The Effect of Thyroid on Calcium Metabolism, *Proc. Soc. Exp. Biol. and Med.*, 1926, 23, 699.
5. Kramer, B., and Howland, J.: The Quantitative Estimation of Calcium, Magnesium, Phosphate and Carbonate in Bone, *J. Biol. Chem.*, 1926, 68, 711.
6. Moore, A. B.: Discussion: *Proc. Staff Meetings of Mayo Clinic*, 1928, 3, 121.
7. Plummer, W. A., and Dunlap, H. F.: Cases Showing Osteoporosis Due to Decalcification in Exophthalmic Goiter, *Proc. Staff Meeting of Mayo Clinic*, 1928, 3, 119.

TWO METHODS OF INVESTIGATING DISEASES OF THE CORPUS STRIATUM.

BY C. J. MUNCH-PETERSEN, M.D.,

SECOND ASSISTANT AT THE DEPARTMENT,

AND

TH. B. WERNØE, M.D.,

FIRST ASSISTANT AT THE DEPARTMENT,

COPENHAGEN, DENMARK.

(From the Department for Nervous Diseases, Rigshospitalet, Copenhagen; Chief Physician, Prof. Dr. med. Viggo Christiansen.)

THE so-called extrapyramidal system, the corpus striatum in the widest sense, occupies an important position in neurologic medicine. Not only do the physiology and pathology of this part of the brain hold many unsolved problems in general as well as clinically, but at the same time these problems touch to an unusual degree upon those domains of medical science which are outside neurology.

One difficulty which often arises in clinical work is to decide whether or not a certain disease picture contains a "striatal" factor or not. This is especially the case when it may be supposed to have epidemic encephalitis as an etiologic basis, and when there are no indisputable symptoms in favor of an extrapyramidal lesion.

This difficulty might be solved if it were possible to work out a method which demonstrates diseases of the striatum with certainty, even when they cannot be found clinically.

The authors have earlier, and independently of each other, indicated two different methods of investigation which are thought to attain this object.

I. A.L.S.R. (*Adrenalin-Liquor-Saccharum Reaction*) (Munch-Petersen's Method). This test is based upon the fact that a hyperglycemia caused by adrenalin, or by adrenalin administered with glucose, is followed by a rise in the sugar content of the spinal fluid as recovered on lumbar puncture.* This rise depends somewhat on the size of the rise in the blood sugar, but if the latter reaches about 0.16 per cent or more a maximal rise in the sugar of the lumbar puncture fluid is obtained under the experimental conditions given. The normal limits of the rise may be reckoned: upper limit, 0.03 per cent; lower limit, 0.015 per cent. The experiment must be carried out on an absolutely fasting patient, and the puncture for the determination of the rise in the sugar of the spinal fluid must be carried out after $2\frac{1}{2}$ hours.

The test is performed as follows: In the morning (after a 12-hour fast) determinations of the blood sugar and spinal fluid sugar are made. The patient then takes 50 gm. of glucose in water (about 150 cc.), and 5 to 10 minutes later is given a subcutaneous injection of 0.5 mg. adrenalin. A determination of the blood sugar is then made every hour, in order to make sure that the rise is high enough. Two and a half hours after the adrenalin injection the blood sugar and spinal fluid sugar are again estimated. As mentioned, the spinal fluid sugar will normally at this time of the experiment have been increased by 0.015 to 0.03 per cent. One may, for instance, find a fasting value of the spinal fluid sugar of 0.05 per cent to have risen to 0.07 per cent. Under pathologic conditions it is found that this increase may be smaller or greater.

Munch-Petersen,¹ on the basis of a large number of observations, interprets a smaller rise as a definite sign of a direct "striatal" affection. A greater rise may also be due to this, but may also be caused by affections outside of the striatum. It may be, however, that the greater rise is caused by an indirect influence upon the functions of the striatum.

II. B.F.I. (*Binocular Faradic Irritation*) (Wernøe's² Method). This test is based upon the well-known motor influence which is caused when a faradic current is lead simultaneously through the palms of both hands. On account of the contraction of the muscles of the upper extremity we get: (1) pronation, (2) flexion of the wrist joint and (3) flexion of the elbow.

On the basis of numerous experiments, Wernøe believes that the

* A pure glucose-hyperglycemia does not cause any rise, or at any rate, a much smaller rise than the hyperglycemia after adrenalin.

reflex is indicated from the sensory tracts of the lower arm. Furthermore Wernøe is of opinion that the highest point of the reflex must be situated in the striatum: (1) because affections of the cortex do not influence the normal course of the reflex; (2) because the reflex disappears with crossed spinal sensory paralysis; (3) because patients with affections of the corpus striatum, but without symptoms arising in other parts of the central nervous system, generally show atypical or absent movements of the arm on bimanual faradic irritation.

Wernøe has previously shown that faradic irritation also causes a cortically induced inhibitory reflex of the motor functions. This explains various atypical responses in patients with either functional pareses or anesthasias.

Wernøe distinguishes between cortically and striatally induced functional atypical responses. The former cause normal, but increased, reactions, often combined with rhythmical movements of the arms, as the result of cessation of the inhibition or of a discontinuous inhibition from the cortex. The latter cause either decreased, absent or altered, grotesque, writhing and unbalanced movements, very likely because of anomalies in the conduction of the striatum.

In cases of organic, striatal affection, the reflex may, as we have mentioned, be absent, or atypical movements may appear, such as extension of the wrist, supination, extension of the elbow and the like.

Neither of the two methods described here have as yet been so thoroughly tested that they can be called pathognomonically certain in their results. We must especially emphasize that a "normal" reaction does not exclude an affection of the striatum. It would, however, be of great importance in evaluating the methods to examine their reciprocal agreement.

It cannot be expected *a priori* that two methods, so different, should agree entirely in their results. Their mechanisms are too far apart for this. On the other hand, it must be said that agreement in a sufficient number of cases, the nature of the cases being duly considered, will give strong reciprocal support to the postulated use of the two methods, which furthermore in certain cases may be used to supplement each other. In reality we here have two experimental methods, which in all respects are independent of each other, one of them being biologic-chemical, the other more clinical, the aim of both, however, being the same: to prove affections in the corpus striatum.

In the table below 33 cases, examined with both methods, have been collected. In 22 of these cases the two methods agreed well (67 per cent). In 7 cases the result of the two methods did not agree (21 per cent). In 4 cases the agreement cannot be judged (12 per cent).

TABLE 1.—ANALYSIS OF DATA OBTAINED BY THE TWO METHODS.

Num- ber.	Diagnosis.	Spinal fluid.		Quo- tient, per cent.	A.L.S.R. reaction, creased.	A.L.S.R. in- creased.	A.L.S.R. de- creased.	A.L.S.R. normal.	B.F.I. reaction.		Remarks.	Correlation of tests.	
		C.	Glob. Alb.						Atypical.	Normal.		Agree- ment	Dis- agree- ment
1.	Encephalitis (chronic)	2/3	0-1-11	64	0.007		+		+		No reflex in spite of max- imal irritation	+	
2.	Encephalomyelitis (chronic)	20/3	2-40	68	0.004		+		+			+	
3.	Encephalomyelitis (chronic)	15/3	0-1-10	68	0.012		+		+			+	
4.	Encephalomyelitis (chronic?)	14/3	2-3-17	71	0.032	+			+		Difference in reflexes, right hand reacts more intensely than the left	+	
5.	Encephalomyelitis (chronic)	3/3	1-13	54	0.010		+		+			+	
6.	Encephalitis	4/3	1-23	73	0.007		+		+			+	
7.	Spondylitis cervicalis tuberculosis	3/3	0-11	65	0.006		+		+			+	
8.	Encephalitis sequelæ	0/3	0-7	65	0.034	+			+			+	
9.	Atrophic lateral- sclerosis	0/3	0-9	45	0.013	+			+		Extension of elbow + rhythmical tremor Flexion of elbow	+	
10.	Encephalitis	5/3	1-2-13	66	0.008				+			+	
11.	Encephalitis	1/3	0-12-19	49	0.045				+			+	
12.	Encephalitis epidemica?	0/3	0-11	55	0.032	++			+			+	
13.	Encephalitis; tremor manuum	0/3	12-16	70	0.011		+		+			+	
14.	Encephalitis (chronic?); paralysis agitans?	1/3	0-9	77	0.004		+		+		Tremor is inhibited	+	

As regards these last cases (Nos. 23, 24, 25, 26) the B.F.I. reactions observed were of such a kind that so far they must be called "functional," whereas the A.L.S.R. showed definite divergence from the normal.

While one would be most inclined to look upon an abnormal A.L.S.R. as a symptom of organic disease, the B.F.I. reactions which have so far been grouped as "functional" are not yet clearly defined. Among other things the location of the affection plays a part, and also the reciprocal collaboration of the cortex and the striatum in each given case.

In the 7 cases in which the disagreement was evident the grouping according to the nature of the symptoms is of some interest.

Without considering the central localization of these two reactions, a subject about which we know nothing, we are justified in supposing that the A.L.S.R. is released by vegetative functions, while the B.F.I. is released *via* motor centers. In 3 of the disagreeing cases the clinical symptoms were essentially of a motor nature (Nos. 27, 31, 32). Here we found a normal A.L.S.R. but an atypical B.F.I.

In 2 other cases of this group (Nos. 29, 30), in which vegetative symptoms were the essential ones, the results were just the reverse. On the whole, atrophy of the striatum seems often to show normal A.L.S.R., at any rate in the first stages. In this respect the 3 cases of paralysis agitans, which have been examined by both methods, are interesting (Nos. 17, 18, 19). The abiotrophy seems so selective in these cases that neither the vegetative functions nor the striatal tracts of the arm reflexes are disturbed by the morbid processes, as in these patients we found normal A.L.S.R. as well as B.F.I. (No. 34, A.L.S.R., normal). On the other hand, in postencephalitic cases of Parkinsonism an abnormal result of both the reactions seems to be the rule, probably because the inflammatory process attacks in the brain tissue far more diffusely than does the abiotrophy. This, moreover, speaks in support of the opinion stated by Viggo Christiansen at the Neurologic Congress in 1920 in Paris—that postencephalitic Parkinsonism and that of paralysis agitans are two quite separate morbid units.

Last, Case 7 is of special interest. In this patient, who suffered from a cervical spondylitis with radicular symptoms, there were no clinical signs of an affection of the striatum. The decrease in the A.L.S.R. and the atypical B.F.I., which quite unexpectedly were found in this case, are therefore instructive in several respects. In the first place, the uniform result of the reactions in this concrete example illustrates the support which mutual agreement means to the judgment of the value of each single method. Even though it is not the rule that abnormal reactions are found in cases of affections of the spine or in juxtaspinal affections, a finding like the one mentioned will nevertheless cause doubt as to the utility of a single

method. It is another matter when two different methods both show results which point in the same direction. In the second place, we see how the methods, alone, or especially when combined, may give us information of an affection of the striatum, which we are not able to recognize with the clinical examination alone. In the third place, these circumstances show us a use of the methods beyond the purely diagnostic one. Granted that these two methods are taken up for clinical use, the possibility appears of an investigation of a more theoretical kind of different groups of diseases, not only in neurology and psychiatry, but also in different types of diseases belonging to other phases of medicine. For, by these methods it may be possible to determine the presence of a striatal component in a given facies morbi.

Considering the importance of the striatal part of the brain in numerous pathologic conditions, circumstances which are as yet not very clear, valid examinations of this kind may be said to be of importance.

Summary. A comparison of the Munch-Petersen and Wernøe tests of function of the corpus striatum has been made in 33 cases. In 22 cases the tests showed good agreement; in 4 circumstances prevented a comparison and in 7 the results were not in agreement. The nature of the disagreement in the last group is discussed and the value of the use of both tests emphasized in giving information about possible lesions of the corpus striatum.

REFERENCES.

1. Munch-Petersen, C. J.: Acta med. scand., 1930, 74, 31, 235.
2. Wernøe: Th. B.: Acta psychiat. et neurol., 1931, 6, 107.

A COMBINED NEEDLE AND CANNULA FOR THE ADMINISTRATION OF TRANSFUSIONS, AND INTRAVENOUS AND SUBCUTANEOUS INFUSIONS.

BY ARTHUR S. W. TOUROFF, B.S., M.D.,

ADJUNCT ATTENDING SURGEON, MT. SINAI HOSPITAL, NEW YORK CITY.

(From the Surgical Service of Dr. Harold Neuhof, Mt. Sinai Hospital.)

IN medical and surgical practice the occasion to perform transfusions or to administer fluids subcutaneously or intravenously over prolonged periods of time frequently arises. The various types of rigid sharp-pointed steel needles which are commonly employed in these procedures have the great disadvantage that inadvertant motion on the part of the patient when the needles are *in situ* may cause local trauma and often pain. When a patient who is receiving intravenous therapy becomes restless or uncoöperative the needle is

often displaced from the vein or may have its point forced through the wall of the vessel. The inevitable result of either of these accidents is the occurrence of perivenous hemorrhage and infiltration, which often is not only painful but may also occasionally result in local tissue necrosis if certain solutions are employed. In those instances in which it is necessary to expose the vein surgically and fix a rigid metal cannula in place, the same dangers exist. In an effort to prevent these unfortunate occurrences, after the needle or cannula has been introduced, the patient's extremity frequently is fixed in an immobilizing device such as a splint. Thus, because of certain undesirable features inherent in the conventional instruments, lacking more perfect equipment we are forced to add to the discomfort of patients already ill.

In an effort to obviate the disadvantageous features of the hypodermoclysis and the intravenous needle, as well as the intravenous cannula, we planned to supplant these three by a single new instrument which we felt should possess the following qualities: (1) It should not have a sharp point capable of traumatizing the vessel wall or causing penetration as a result of motion on the part of the patient. (2) It should be flexible for the same reason. (3) It should not be readily displaceable. (4) It should lend itself readily to introduction subcutaneously and to introduction intravenously, by venipuncture or surgical exposure. (5) It should resemble the conventional instruments, so that any one accustomed to their use would be able to employ it readily, without the necessity of adopting a new or complicated technique.

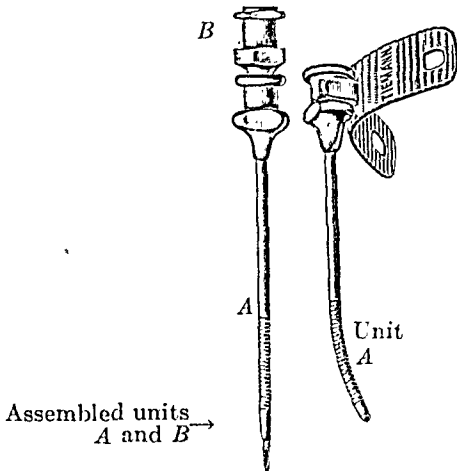
With these objects in view, we have devised an instrument which fulfills the necessary requirements and which in actual practice has proven satisfactory. It consists of two parts, which we shall arbitrarily designate as Unit A and Unit B. Unit A represents the true instrument, while Unit B is employed merely to facilitate the introduction of the former.

Unit A resembles somewhat an ordinary No. 12 gauge intravenous needle with a shaft 2 inches long. The proximal $1\frac{1}{4}$ inches of the shaft is rigid and ends in a hub which fits a Luer syringe. The distal $\frac{3}{4}$ inch of the shaft, however, is flexible and is so constructed of fine, closely-coiled silver wire that it can readily be bent even on slight pressure. The tip of the instrument instead of being sharp and bevelled is blunt and rounded.

Within the lumen of Unit A there snugly fits a conventional No. 20 gauge sharp-pointed, rigid Luer needle which we have designated as Unit B. When the two units are assembled this second needle (Unit B) is sufficiently long to project for a short distance beyond the tip of Unit A. The two units fit one another accurately, so that no special locking device is needed. The purpose of Unit B is as follows: (1) To act as a stylette, in order to render the instrument rigid during introduction into a vein or beneath the skin. (2) To supply a sharp point to the instrument,

in order to facilitate its introduction. (3) To enable one to draw blood with a syringe from the vein, while introducing the instrument by puncture, and thus to make certain that it has been accurately introduced.

After the assembled instrument has been introduced, the inner rigid needle (Unit B) is withdrawn leaving only the outer flexible needle (Unit A) *in situ*. The instrument should always be introduced for a distance of at least 1 inch, so as to prevent leakage which may sometimes occur through the interstices of the distal, flexible $\frac{3}{4}$ -inch segment, if motion on the part of the patient should accidentally acutely angulate it. When employing the instrument for hypodermoclysis or intravenous infusion by puncture, it must be introduced with both units assembled, for the reasons stated above. On the other hand, when employing it for intravenous infusion by surgical exposure of the vein it is necessary to introduce



Unit A only. After introduction, fixation *in situ* is facilitated by means of a readily applicable snap clip which grasps the hub and which presents two lateral wings of flexible metal for broad approximation to the skin by means of a tape or adhesive straps.

In actual practice the instrument possesses the following attributes: (1) It may be used for transfusion, hypodermoclysis or for venoclysis, by puncture or surgical exposure. (2) It is less apt than the conventional type of needle to cause trauma or penetration of the vessel wall, with resultant perivenous hemorrhage and infiltration. This is so because of its flexibility and the fact that it bears a blunt rounded point. (3) It is not as readily displaceable as the conventional type of needle, because the ribbed outer surface of the distal flexible segment tends to prevent accidental slipping. (4) Its mode of introduction differs in no respect from that of the conventional types of needle or cannula.

NOTE.—This needle is manufactured by George Tiemann & Co., New York City.

REVIEWS.

HUMAN CANCER. By ARTHUR PURDY STOUT, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. Pp. 1007; 331 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

"THIS monograph . . . is an attempt to discuss the development and growth of all of the different kinds of cancer in the human body. It has long been recognized that each particular anatomical region of the body produces cases which differ in many respects from those in other parts of the body. Therefore this book deals with cancer by regions. Although not universally accepted, the idea that chronic irritation is an important factor in etiology enjoys a wide popularity at this time. For clarity and convenience in discussion it has been accepted as a working hypothesis, the description of every cancer is preceded by a section labeled 'etiological factors and precancerous lesions,' in which is collected all of the information which could be found bearing upon the relationship between the action of the so-called 'chronic irritants' cellular hyperplasias including benign neoplasms, and cancer. The reader must judge whether sufficient evidence has been offered to make this hypothesis tenable or not.

"No attempt has been made to discuss the chemical aspect of neoplasms, the biological differences between cancer cells and normal cells and the biochemical effects of cancerous growth upon the body." Most phases of experimental cancer research have also been omitted.

In the introduction certain important matters are carefully considered. For example, under "Precancerous Lesions," the author says, "In some ways this has been an unfortunate term because it has connoted in many minds the *inevitable* sequence of events. Such, of course, is very far from the truth; if it were true, the human race would long ago have become extinct. . . . By precancerous, therefore, is meant simply a condition which may be associated with the development of cancer."

Another point discussed is the "Criteria of Cancer" upon which there is much uncertainty today that one pathologist considers a tumor malignant which another calls benign. In order that there shall be no misunderstanding of what the author thinks, he generalizes thus: "A cellular proliferation is probably not a cancer, unless one finds *both* the morphological changes of the individual cells which are found in undoubted cancers and also evidences of infiltrative growth outside of the usual anatomical boundaries of whatever type of cell happens to be under consideration."

With this interesting beginning the real book begins with "The Oral Cavity," and here the heart of the Reviewer fails him, for a definite program for arranging the text now appears. We find that the oral cavity consists of the lips, tongue, floor of the mouth, cheeks, gums of the mandible, upper oral cavity and posterior oral cavity, for each of which all of the possible tumors are to be considered with reference to etiology, spread, symptoms, diagnosis, prognosis, treatment. Then follows the same for the dental apparatus, the salivary glands, the esophagus, the stomach, the liver and

intrahepatic bile passages, the gall bladder and extrahepatic ducts, the pancreas and ampulla of Vater, the intestine and rectum, the appendix, the peritoneum, omentum, mesentery and retroperitoneal tissues. This occupies 248 pages, to be followed by similar treatment of the mammary gland, the uterus, the vulva and vagina, the female urethra, etc.

Such an arrangement makes the work a book of reference, and as such it is excellent and very useful, but it almost destroys its readability.

Both author and publisher are to be congratulated in having produced a handsome, beautifully illustrated and highly useful book along lines that are unconventional.

J. McF.

LIVING THE LIVER DIET. By ELMER A. MINER, M.D., Independence, Kan. With an Introduction by WILLIAM P. MURPHY, M.D., Instructor in Medicine at the Harvard Medical School, Boston. Pp. 108; 3 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$1.50.

A LITTLE diet manual for the pernicious anemia patient which will find its chief value in the numerous recipes and in the enthusiastic manner of presentation by the author, himself afflicted with the disease. R. K.

OSLER AND OTHER PAPERS. By WILLIAM SYDNEY THAYER, M.D., LL.D., DR. HON., Sc.D., F.R.C.P. (IRE.) HON., Professor Emeritus of Medicine at The Johns Hopkins University. Pp. 386. Baltimore: The Johns Hopkins Press, 1931. Price, \$3.50.

ONE of Osler's greatest attributes was unquestionably his ability to harmonize groups in which he was active and to stimulate younger men to enthusiastic, constructive work. It is fitting that one who gratefully acknowledges his great debt should produce this volume, which is in part at least a notable tribute to "the Chief." But it is even more valuable as a collection—incomplete, unfortunately—of writings of one of the most charming medical essayists of our time. One does not have to read many pages before appreciating what a trenchant evaluation with illuminating sidelights this is of a great medical figure that none but the author could have given. Still more is one eventually impressed by the fact that the clear graceful periods are conveying *tute et jucunde* invaluable maxims to students of medicine and to the medical profession at large. If our profession in this country could be more under the guidance of such pure-minded, penetrating artists, there would be less call for wringing of medical hands, advice of often self-appointed efficiency experts, and the expensive fact-finding of investigating committees. As in the author's quotation from Monna Vanna, "Each man sees in another individual that which he sees in himself and each one comprehends the other individual in a different fashion and precisely from the level of his own moral nature;" so too the reader learns much about the writer as he proceeds.

Of the 24 essays, the first 15 are directly connected with Osler; numbers 7, 8, 14, 15, 16, 20 and 22 are inspiring addresses to boys of all ages, chiefly medical; while Cotton Mather, Laennec, Bright, Fitz, Welch and Howland are subjects of semibiographical sketches. But why attempt vivisection of a living unit? The book can be read from cover to cover, as I did, or any of its component parts may be selected, and with either method pleasure and profit are guaranteed.

E. K.

A DOCTOR OF THE 1870's AND 80's. By WILLIAM ALLEN PUSEY, Sometime President of the American Medical Association and of the American Dermatological Association. Pp. 153; illustrated. Springfield, Illinois: Charles C Thomas, 1932. Price, \$3.00.

ALTHOUGH writing the biography of the father for whom one had a "boundless respect and affection" may be as difficult as achieving an accurate autobiography, in the present case success has been accomplished. The author not only tells an interesting story sympathetically but obviously has accurately portrayed the daily existence of a flourishing country doctor in an average rural community of the previous generation but of an age that has passed. Before bacteriology had had time greatly to influence medicine and surgery (and the elder Pusey is admitted not to have grasped its significance) and before the telephone and automobile had revolutionized country practice, this austere, wise, keen and courageous practitioner took adequate care of the health of his community and lived a full life of the kind that has contributed so largely to making our nation what it is. As a counterfoil to the unrealities of the country doctor of fiction, this figure contributes an historical record of value. E. K.

CONQUERING ARTHRITIS. By H. M. MARGOLIS, M.D. Pp. 188; 2 illustrations. New York: The Macmillan Company, 1931. Price, \$2.00.

THE author has attempted a difficult thing and can hardly be said to have succeeded. The first 120 pages take up the question of classification of the chronic arthritides and a description of rheumatic fever. In this description of the varieties of arthritis which is a departure from accepted classifications, gout, a condition admittedly uncommon in America at least, occupies 12 pages. Atrophic arthritis is inadequately designated "infectious" arthritis. The author devotes several pages to the influence of sympathectomy on the condition, avowedly a measure of last resort. The sections on blood chemistry and on the bowel in arthritis show only a superficial acquaintance with the literature on these subjects. The sections on nonspecific protein and vaccine are very well done. The diet recommended in "infectious" arthritis is high in calories and unrestricted in other respects: this is not a reflection of the opinion of the best authorities. The book is somewhat verbose and filled with rather loose optimism. On the whole the patient who trusts to this book will not be safely guided through the mazes of arthritis. E. P.

PRACTICAL MORBID HISTOLOGY. By ROBERT DONALDSON, M.A., M.D., CH.B. (EDIN.), F.R.C.S.E., D.P.H., Sir William Dunn Professor of Pathology in the University of London, etc. With Foreword by SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., Regius Professor of Physics, University of Cambridge. Pp. 487; 214 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1931.

"WITH the ever-expanding scope of pathological science, the attractions of bacteriology, immunology and biochemistry, and the increasing demands on the time of the hard-worked medical student, there has arisen a real danger that changes in structure, as seen with the naked eye in the postmortem room and under the microscope in the laboratory, which are so inseparably bound up with functional reactions, or symptoms, may receive insufficient attention. A practical knowledge of morbid anatomy is an essential basis for the understanding and interpretation of the physical signs of disease,

and so for a correct diagnosis, and also in connection with the further and more difficult problem of prognosis. Experience gained in the postmortem room of what are the common pathological changes engenders a sense of due proportion in estimating the character, extent and associations of structural changes in a given case, and such a training checks fanciful guesses and hypothetical diagnoses. Neglect of the study of structural change may naturally result from realization of the importance of recognizing and investigating the earliest departures from the normal and functional disorders; this tendency should be corrected by Professor R. Donaldson's clear account of the morbid changes of structure in this enlarged second edition enhanced in value by numerous illustrations."

(Extract from Sir Humphry Rolleston's Foreword.)

PRACTICAL ENDOCRINOLOGY. By HENRY R. HARROWER, M.D. Pp. 704. Glendale, California: Pioneer Printing Company, 1931. Price, \$5.00.

As a reference book (for which it is primarily intended) and used in the right way, this book should prove extremely useful in a field, which though often cultivated by methods of dubious value, is admittedly of the very greatest importance. The author's familiarity with the subject is evinced in an interesting 20-page chronological list of "endocrine events;" and yet this also brings out a weakness of the literature in this field in that it records a number of discoveries of doubtful or even rejected value. - Under the four headings of Fundamentals, Principles, Diagnostics and Therapeutics, the actions of some 16 organs are considered as applied to a wide range of human ills. In the section on the stomach of the chapter on Principles, such preparations as gastrin, gastrin, myogestin and ventriculin are considered; while under the spleen we read of lienin, stagnin, hormonal, colloidogenin, splenocin and other little known substances. From one point of view this may be looked on as adding to the value of the work as a reference book. Considerably more than half the book is devoted to therapeutic considerations.

E. K.

THE VITAMINS. Monograph of the Pickett-Thomson Research Laboratory, Vol. I, September, 1931. By ETHEL BROWNING, M.D., Liverpool, Assistant Pathologist to the Pickett-Thomson Research Laboratory, St. Paul's Hospital, London. Pp. 575; illustrated with figures and tables. London: Bailliere, Tindall & Cox. In America, Baltimore: The Williams & Wilkins Company, 1931.

This book is a very complete compilation of the material on the vitamins. One especially commendable feature is the emphasis laid upon the pathological lesions associated with the avitaminoses. It is to be regretted, however, that with a wealth of material from which to select illustrations of the histopathology, so much space should be given to lesions produced by "bad diets" and relatively so little to specific changes.

E. W.

COURTS AND DOCTORS. By LLOYD PAUL STRYKER. Pp. 236. New York: The Macmillan Company, 1932. Price, \$2.00.

MR. STRYKER, having been for many years general counsel for the Medical Society of the State of New York, is well prepared to write a book of this kind. The book itself is a much needed guide for physicians in their

relation to the law—their duties and rights as citizens. Government has become so paternal and bureaucratic that physicians, and indeed all citizens who engage in any business or profession must know much more about legal matters than formerly in order to keep out of trouble.

The changed attitude of the people about the function of government has led to evil, not to good. The founders of the Republic regarded government simply as a necessary evil and hence they restricted its duties merely to police work and taxation. The newer attitude, that people are made for the state, that the state is to be a nursing mother, to "give buns to the people who have no teeth," to make an environment for the unfit at the expense of the fit, to make them happy, has made life so complicated and laws so multitudinous that no physician can live today without employing a lawyer to look after his interests. Blackmail, malpractice suits, the narcotic and prohibition laws, and the bureaucratic attitude of government officials make a book like this necessary for every physician. C. B.

HISTORY OF MEDICINE IN THE PROVINCE OF QUEBEC. By MAUDE E. ABBOTT, B.A., M.D. Pp. 97; 41 illustrations. Montreal: Medical Museum, McGill University, 1931. Price, \$3.00.

THIS outline of Quebec medicine is reprinted with additions from "The Storied Province of Quebec." The first half tells of primitive Canadian medicine, the struggles of the early French colonists, and the rise of the French hospitals from a different point of view, to be sure, but in considerably less detail than does Heagerty's "Four Centuries of Medical History in Canada" (see review in *Am. J. Med. Sci.*, 1929, 178, 270). The latter half, especially those pages dealing with the Montreal General Hospital and McGill University and the present situation, progresses more firmly and entertainingly. The paper and some of the illustrations are regrettably poor; yet we recommend the reading matter highly to those interested in the subject. E. K.

HERZ UND ANGST. By PROF. DR. LUDWIG BRAUN. Pp. 119. Wien Franz Deuticke, 1932. Price, M. 6.—.

A CONTINUATION of *Herz und Psyche*, published by the author in 1920, this essay, based on observation of the sick, analyzes "anxiety" (Angst) from the etymologic, clinical, physiologic, diagnostic and phylogenetic points of view. Committed to the theory that the sensation of anxiety is a specific sensation of the heart, it finds copious support in literature and ancient science even before Aristotle's enunciation that the heart was the seat of the mind. In modern times fewer quotations are available. The author is content with such assertions as that we may remain quiet in the face of great emotion or danger, until suddenly we are overcome with anxiety due to the occurrence of abnormal sensations in the heart. E. K.

FEMALE SEX HORMONOLOGY. By WILLIAM P. GRAVES, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School; Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline. Pp. 131. Philadelphia: W. B. Saunders Company, 1931. Price, \$3.50.

THIS book consists of a review of the enormous amount of work which has been done in isolating and evaluating the various female sex hormones,

bringing together in one small volume a well-digested summary of our present knowledge of this complex subject. Since these studies have introduced into medical literature a host of new words, the inclusion of a glossary which well defines them is a most welcome item and for those who wish to go further into the subject an excellent bibliography is appended. Organotherapy is considered purely from the scientific aspect in a most conservative manner, with no specific recommendations as to dosage or product, but rather indicating the limitations of such therapy at the present time. Some of the contained information may be of little value a few years hence, since this subject is in the formative period, nevertheless it is an excellent résumé and is of the same standard as the author's literary contributions.

F. B.

NUTRITION ABSTRACTS AND REVIEWS. VOL. I, Nos. 1 and 2. October, 1931. Issued under the direction of the Imperial Agricultural Bureau, the Medical Research Council and the Reid Library. Pp. 351. Aberdeen: The Aberdeen University Press, Ltd., 1931. Price, 13s.

THIS Journal has as its editors the well-known scientists, John Boyd Orr, J. J. R. Macleod, Harriette Chick and corresponding editors from centers throughout the world. Its purpose is to collect abstracts of all literature bearing on nutrition of man and of farm animals. More than 450 journals are reviewed. A number will deal with the present state of knowledge of different aspects of the subject, giving a bibliography of the literature. Others will be devoted to articles of a more general nature stating a point of view. There are also book reviews.

The abstracts are arranged under the following headings: Technique; composition of foodstuffs; physiology of nutrition; dietetics; feeding of animals; diet in relation to health and disease. There is an author's index and also an index of the contents.

The abstracts in the present number are concise and give the essential facts of the articles reviewed. Each abstract has the title in the native language and if foreign, an English translation, the number of references, graphs, illustrations and the institution from which it comes. In view of the rapidly increasing literature in this field, the journal should be a great aid to those interested in the subject.

The annual price is 21 shillings. However, no mention is made of the number of issues per year.

L. J.

GROWTH IN PRIVATE SCHOOL CHILDREN. By HORACE GRAY, Stanford University Hospital, San Francisco, and J. G. AYRES, The Institute for Juvenile Research and Behavior Research Fund, Chicago. Pp. 282; illustrated with figures and tables. Chicago: University of Chicago Press, 1931. Price, \$3.50.

FUNDAMENTALLY this book presents the carefully compiled results of 4583 sets of measurements (3110 of boys and 1473 of girls) of private school children, classified by age groups from 1 to 19 years. The set includes weight, 17 linear measurements, 17 indices related to stature and 8 other indices. Standard deviations and coefficients of variation are given for each of the 43 items by sex and age group.

The material affords basal data which the pediatrician versed in the terminology of elementary statistics can readily use in estimating the development of a child in his care. To the young contemporary worker

in this field the chapters on anthropologic and statistical method, on body types, on sexual, racial, age and economic differences will be found most instructive and the bibliography most useful. Above all, the book is a record of anthropologic research and observation which will one day be an historical document.

In the chapter on Race the author, judging by the percentage of replies received in response to his short questionnaire, concludes that the East is third and last in showing interest in schools and children. Due to a discrepancy between table and text, it is not clear whether it is Chicago or California which leads.

C. M.

A DESCRIPTION OF THE PLANES OF FASCIA OF THE HUMAN BODY. By B. B. GALLAUDET, M.D., Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York. Pp. 75. New York: Columbia University Press, 1931. Price, \$2.00.

THIS small volume represents the results of an intensive study of the fascias of the human body, by a highly trained anatomist of many years' experience in the dissecting room. The main thesis is that the fascial planes constitute a continuous sheet of connective tissue, varying in thickness and density according to location. The numerous separately named fascias of the textbooks are all discussed, and comparisons are made with the author's observations in 34 bodies, dissected solely for this study. Special attention is paid to the fascial planes of the abdomen, pelvis and perineum, and critical descriptions of these are given.

W. A.

THE RENAL LESION IN BRIGHT'S DISEASE. By THOMAS ADDIS, Professor of Medicine, Stanford University, and JEAN OLIVER, Professor of Pathology, Long Island College of Medicine, Formerly Professor of Pathology, Stanford University. Pp. 628; 170 full page plates, 2 in color; 21 illustrations and 1 folding table. New York: Paul B. Hoeber, Inc., 1931. Price, \$16.00.

THIS splendid book is the coöperative work of a clinician and a pathologist, both well known students of Bright's disease. It is not a mere review of the literature but rather an account of the personal studies of the authors. The chief aim is correlation between clinical and morphologic facts, that is to say between carefully studied functional and structural disturbances. For too long a time have pathologic physiology and pathologic anatomy been divorced, to the great harm of either discipline. In this book, as in the great work by Volhard and Fahr on renal disease, the functional and structural changes are successfully regarded not as separate subjects but as integral interrelated parts of Bright's disease. The authors point out that Bright himself stressed that disease must be interpreted by "A reference to morbid anatomy." With this aim in view the authors present a very careful analysis of about 100 cases, all of them personally investigated by methods designed to permit correlation between the clinical and the morphologic observations. There is given an excellent description of the clinical methods elaborated to determine the degree of renal function, and the nature and extent of the renal lesions. Similarly, the purpose and the technique of the pathologic methods are clearly presented, and the meaning of the clinical and pathologic terms employed are rigidly defined. A very valuable part of the work is the complete presentation of many case reports. The structural changes are beautifully illustrated by micro-

photographs. There are chapters on the classification and theory of Bright's disease, and on the course and sequence of the pathologic processes in this disease.

The work can highly be recommended to physicians and pathologists who desire a thoroughly modern presentation of Bright's disease.

B. L.

PHANTASTICA, NARCOTIC AND STIMULATING DRUGS. By LOUIS LEWIN. Pp. 335. New York: E. P. Dutton & Co., 1931. Price, \$3.75.

THIS volume, the first of its kind, tells in a fascinating way of the drugs and substances that man—civilized and savage—seems always to have used to soften his sorrows and to add to his pleasures.

Comprehensive consideration is here given of narcotic and stimulating drugs which are classified as follows: (1) Euphorica: substances which inhibit the functions of emotion and perception, giving physical and mental comfort, including morphin, cocain, etc. (2) Phantastica: cerebral excitants that bring about hallucinations and illusions; mescal buttons and Indian hemp represent the series. (3) Inebriata: such as alcohol, chloroform, ether and benzin, which primarily cause cerebral excitation later to be followed by depression or possibly by cessation of function. (4) Hypnotica: somnolent substances, such as chloral, veronal and sulphonal. (5) Excitanta: mental stimulants which do not cause a change in consciousness; these are vegetable substances like caffen, tobacco and betel.

The soul is mentioned with recurring frequency—13 times. Is this unlucky for science, for metaphysics or for neither? There is a tone of pessimism in the book which is a bit disturbing; doubtless the use of narcotic substances is increasing absolutely but perhaps not so much relatively. This is a world of change and there is easily a chance of a change for the better.

N. Y.

BOOKS RECEIVED.

NEW BOOKS.

The Sign of Babinski. By JOHN F. FULTON, Sterling Professor of Physiology in the Yale University School of Medicine, and ALLEN D. KELLER, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. Pp. 165; 65 illustrations. Springfield, Illinois: Charles C Thomas, 1932. Price, \$5.00.

Individuality of the Blood. By PROF. LEONE LATTES, Director of the Institute of Forensic Medicine in the University of Modena. Translated by L. W. HOWARD BERTIE, M.A., B.M., B.Ch. (Oxon.), from the French edition 1929. Pp. 413; 71 illustrations. New York: Oxford University Press, 1932. Price, \$7.50.

Diabetes in Childhood and Adolescence. By PRISCILLA WHITE, M.D., Physician at the New England Deaconess Hospital, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. Pp. 236; 25 illustrations, 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, \$3.75.

The Use of Lipiodol. By J. A. SICARD, Late Professor in the Faculty of Medicine, Paris, and Physician at the Necker Hospital, and J. FORESTIER (Aix-les-Bains). Pp. 235; 50 illustrations. New York: Oxford University Press, 1932. Price, \$4.00.

- The Medical Annual 1932. Jubilee Volume, 50th Year.* By various contributors. Edited by CAREY F. COOMBS, M.D., F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 674; 179 text illustrations and 81 plates, plain and colored. Bristol: John Wright & Sons, Ltd., 1932. Price, 20/- net. American publisher: William Wood & Co., Baltimore. Price, \$6.00.
- International Studies. Medicine and the State.* Conducted for the Milbank Memorial Fund. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. With a Foreword by WILLIAM H. WELCH, M.D., LL.D. Pp. 300. Baltimore: The Williams & Wilkins Company, 1932.
- The Nature of Disease Journal, Vol. I.* By J. E. R. McDONAGH, F.R.C.S. Pp. 171. London: William Heinemann, Ltd., 1932. Price, 7/6 net.
- Accidents, Neuroses and Compensation.* By JAMES H. HUDDLESON, M.D., Associate in Neurology, Columbia University; Attending Neurologist, Neurological Institute, New York. With a Foreword by J. RAMSAY HUNT, M.D., Sc.D., Professor of Neurology, Columbia University. Pp. 256. Baltimore: The Williams & Wilkins Company, 1932. Price, \$5.00.
- International Studies. Prevention and Treatment of Disease, Vol. III. England and Wales, Scotland and Ireland.* Conducted for the Milbank Memorial Fund. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 558; illustrated with tables. Baltimore: The Williams & Wilkins Company, 1932. Price, 16s.
- The Medical Clinics of North America, Vol. 16, No. 1 (Philadelphia Number, July, 1932).* Pp. 290; 75 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, Paper \$12; Cloth \$16.
- Nosokomeion. Quarterly Hospital Review.* Second Special Number, containing the proceedings of the Second International Hospital Congress. Pp. 313. Stuttgart: W. Kohlhammer, 1932. Price, 11.25 Marks.
- Quantitative Clinical Chemistry, Vol. 2, Methods.* By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University, School of Medicine, and DONALD D. VAN SLYKE, Ph.D., Sc.D., Member of The Rockefeller Institute for Medical Research. Pp. 957; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$10.00.

NEW EDITIONS.

- The Chemistry of Tuberculosis.* By H. GIDEON WELLS, M.D., Ph.D., Director of the Otho S. A. Sprague Memorial Institute, and Professor of Pathology in the University of Chicago, and ESMOND R. LONG, M.D., Ph.D., Director of the Laboratory of The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, and Professor of Pathology, University of Pennsylvania, formerly Professor of Pathology in the University of Chicago. Pp. 481; illustrated with tables. Second edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1932. Price, \$7.00.
- Manuale di Analisi Chimica.* By CESARE SERONO, Dottore in Medicina ed in Chimica; Docente in Chimica e Microscopia Clinica Nella R. Università di Roma. In collaboration with PROF. ALFONSO CRUTO. Pp. 483; 85 illustrations. Second edition. Torino: Unione Tipografico-Editrice Torinese, 1932.
- The Anatomy of the Human Orbit.* By S. ERNEST WHITNALL, M.A., M.D., B.Ch. (OXON.), M.R.C.S., L.R.C.P. (LOND.), Professor of Anatomy, McGill University, Montreal. Pp. 467; 212 illustrations. Second edition. New York: Oxford University Press, 1932. Price, \$6.25.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Arterial Atony and Arteriosclerosis.—PLESCH, Professor of Internal Medicine in the University of Berlin (*Lancet*, February 20, 1932, p. 385) advances the thesis that arteriosclerosis is only a part of a general constitutional systemic disease which affects particularly unstriated muscle and attaching the whole vascular system simultaneously. It is a disease which sets in at a comparatively early age, which can be arrested and cured in the early stages, according to Plesch's ideas, and in which the local arteriosclerotic changes such as calcification, represents purely a defensive mechanism. The arteriosclerosis of old age due to wear and tear shows local calcified areas, whereas arteriosclerosis is a disease which at the onset at least involves simultaneously and equally the entire vascular tree. That these two types differ clinically is a well known observation. The primary etiologic factor responsible for true arteriosclerosis is a weakening of the muscular and elastic elements of the blood vascular walls. They become stretched and dilated at such points that are exposed to dynamic pressure so that histologic changes occur, serving to raise the resistance of the walls. This pathologic change is ultimately completed by the deposition of lime plates so that calcification and ossification of the vessel represents not another disease but a healing process. Plesch's ideas are substantiated by certain pathologic-anatomic observations and by certain etiologic, statistical, experimental and clinical proofs. It would be impossible to detail all these data that Plesch has given to maintain his thesis. Certainly if they are taken individually and collectively they represent a large group of phenomena which might explain the occurrence of arteriosclerosis as a disease which depends primarily upon atony of the arteries. Although it is possible to view with acquiescing interest the ideas Plesch has concerning the mechanism of the production of arteriosclerosis it is however difficult to accept, except with a certain amount of skepticism, his ideas concerning therapeutics and the cure of arteriosclerosis. He suggests for treatment, among other things, blood letting at times; the reduction of nitrogen and salt in the diet; rest in the horizontal position thereby relieving the heart, in order to exclude the hydrostatic pressure factor which is an important part of the pathologic

mechanism; a "dietetic day" once a week; and much fresh air. Particularly stimulating is his idea that the majority of cases can be handled without the use of drugs. Digitalis he says is objectionable; cardiac tonics not indicated. Small doses of iodid of potassium are injurious rather than useful. Most drugs that directly affect the vessels are harmful. His one therapeutic suggestion is when arteriocalillary fibrosis has already developed iodid of potassium in doses up to 8 gm. daily should be ordered for 10 days disregarding any symptoms of iodism.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

The Treatment of Syphilis.—GOUIN, BIENVENUE and DAOOLAS (*Urol. and Cutaneous Rev.*, 1931, 25, 770) say that the application of the leukocyto-reaction is indicated as a means of diagnosis in suspected syphilis where the serologic reactions are mute and the clinical evidences doubtful. The leukocyto-reaction will also be indicated for gauging from time to time the drug used. The reactions of the body against the disease, or the drugs, change in effect either spontaneously or by the evolution of the disease or by treatment. All syphilologists know the variations of resistance of syphilis, the variations in the action of a drug in a given subject, as well as the variations in tolerance. If one only utilizes the adequate drug one will avoid bad or useless treatments or a mixed series used blindly. Finally the leukocyto-reaction will be indicated for determining the termination of antisymphilitic treatment, that is to say, if the patient is cured and to test this cure by different salts. A leukocyto-reaction remaining positive demonstrates the necessity of continuing intermittent treatment.

Interparietal Hernias.—LOWER and HICKEN (*Ann. Surg.*, 1931, 94, 1070) claim that interparietal hernia is a term used to designate a group of hernias which occur in the inguinal region between the various layers of the abdominal muscles and are classified according to the anatomic location of the hernial sac. Properitoneal hernia includes all those cases in which the hernial sac lies between the peritoneum and the transversalis fascia, 119 such cases being reported. In the interstitial hernia the sac lies between the transversalis fascia and muscles between the transversalis and internal oblique muscles or between the two oblique muscles, 348 such hernias having been reported. In superficial hernia the sac may be monolocular or multilocular, the latter being the form present in the majority of cases. The usual clinical picture is that of intestinal obstruction. Treatment consists of early recognition and immediate relief by operation.

Suprapubic Prostatectomy.—LONSLEY and KERWIN (*J. Am. Med. Assn.*, 1932, 97, 1669) believe that the surgeon operating on the prostate must adopt the procedure employed to the special needs of the patient

involved; there can be no routine technique applicable to all cases. Suprapubic prostatectomy is a one-man operation, while perineal prostatectomy requires coöperation of a trained team. If the prostatic hypertrophy has dilated the internal sphincter, enucleation of the gland is better done by the suprapubic route. When the enlarged gland has remained within its natural anatomic limits it can be reached more safely and conveniently by way of the perineum. The authors prefer the technique of suprapubic prostatectomy devised by Freyer more than 30 years ago, whose procedure consisted of enucleation of the gland through an incision in its capsule, using the finger to detach it from the capsule and observing great care not to injure the plexus of Santorini, situated at the top of the vesical sphincter, as such injury is likely to induce severe hemorrhage. As suprapubic enucleation is prone to tear the mucosa from the verumontanum, thus exposing the orifices of the ejaculatory ducts to infection, a bilateral vasectomy should always accompany suprapubic prostatectomy. Preliminary drainage is a prerequisite to successful prostatectomy, but may be accomplished in a number of ways according to the needs of the individual patient. Cystotomy employing MacGowan's transverse incision, vesical puncture with Kidd's instrument and the indwelling catheter have all given satisfaction on different occasions.

Primary Tuberculosis of the Parotid Gland.—BOWMAN and FLIN (*Ann. Surg.*, 1932, 95, 52) state that tuberculosis of the parotid gland is rare and is often mistaken for malignancy, such as syphilis or mixed tumor. Two distinct types are usually found: (1) Chronic or fibroid type, which is encapsulated and may not produce symptoms for months or even years; (2) a type acutely inflammatory, which is diffuse and runs its course in a few days or a week. Tubercle bacilli gain entrance into the parotid gland by one of three ways: Canalicular, hematogenous or lymphatic, with the first being the most common. Symptoms consist of swelling of the gland either as a circumscribed or fluctuating tumor or more diffuse, with an occasional soft spot. The second type is usually adherent, red, tense, shiny and edematous. Pain is a late sign and the glands of the neck are not involved. Diagnosis is likely to be difficult unless it is confirmed by biopsy. Prognosis is good as the affection is purely local. Treatment is purely operative, and even where facial paralysis takes place from injury to the facial nerve, either by disease or operative trauma, there is recovery in most instances.

Traumatic Necrosis of the Liver.—HELWIG and ORR (*Arch. Surg.*, 1932, 24, 136) write that a case of traumatic pulpification of the liver without rupture is reported in which the patient died after 11 days with an extensive nephrosis (general inflammatory involvement of the kidneys). He was extremely jaundiced and had diffuse hemorrhages into the serous cavities. The output of urine was scanty and the blood nitrogen was greatly increased, particularly the creatin which amounted to 25 mg. per 100 cc. The mechanism of renal necrosis is discussed and the histologic renal picture, as well as the clinical course, would seem to favor the theory that some toxin was elaborated in the liver, through hemorrhagic necrosis, which acted directly on the kidney.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

Decholin Treatment of Melancholia.—On the theory that certain mental disturbances are more or less closely related to functional disorders of the liver, HARTMANN and WEISSMANN (*Med. Klin.*, 1931, 27, 1819) employed decholin intravenously in individual doses of 10 cc. in a group of 16 patients suffering from melancholia. They administered from three to ten injections, the average number being 5 per series. In some patients diarrhea, vomiting and elevation of temperature required the interruption of treatment after three or four doses. Eight of the 16 patients showed either subjective or objective improvement as a result of this treatment. In 5 of them this occurred at once after the administration of decholin. In the remaining 3 the improvement did not develop until after the lapse of a few weeks. One patient showed improvement immediately after the first injection but failed to respond to the subsequent ones. The improvement was purely transitory in 3 patients while in 4 it was so pronounced and lasting as to permit their discharge from care. In the remaining 8 patients of the series no benefit was secured. The authors feel that there is some relation between total doses and the results obtained, and that in general five injections are required to give reasonable promise of satisfactory results. However, 2 patients who received nine and ten injections respectively both failed to show satisfactory results. Those patients in whom the melancholia is associated with anxiety states seem to be decidedly more likely to be benefited by decholin than are the purely depressed types.

Quinidin Therapy in the Treatment of Cardiac Irregularities Due to Hyperthyroidism.—Experience with a large number of patients with hyperthyroidism who have been subjected to thyroidectomy constitutes the basis for the conclusions as to the value of quinidin therapy which are presented by ANDERSON (*Ann. Int. Med.*, 1932, 5, 825). While auricular fibrillation associated with hyperthyroidism tends to disappear following thyroidectomy, the frequency of the spontaneous restoration of normal rhythm varies between 32 and 60 per cent. The postoperative administration of quinidin raises the frequency of return to sinus rhythm to a minimum of 60 per cent and a maximum of 96 per cent. From extensive experience the author concludes that by far the most satisfactory results from quinidin are to be obtained when its administration is begun early, on the third or fourth day postoperative. The usual test doses should precede therapy and the latter should be begun with doses of 0.3 gm. (5 grains) of quinidin administered every 4 hours night and day. This dose may be increased by shortening the interval between administrations to every 3 hours or even to every 2 hours night and day for 1 or 2 days. The proportion of patients who

show idiosyncrasy to quinidin is extremely small in the author's experience and although these patients cannot be continued on the drug this rarely makes them constitute a significant bar to its routine effectiveness in hyperthyroidism.

Experiences With the Use of Metaphyllin Euphyllin, Cheyne-Stokes and Other Forms of Respiratory Disturbances.—On the basis of observations made during the past 8 years with the intravenous administration of metaphyllin for the relief of Cheyne-Stokes respiration and other central respiratory disturbances, VOGL (*Med. Klin.*, 1932, 28, 9) reaches the following conclusions: That metaphyllin given intravenously in doses varying from 0.24 to 0.48 gm. is the most valuable of all agents for the control and relief of most central forms of respiratory distress. It restores respiration immediately where it has been suppressed by anesthesia for which purpose the large dose should be injected rapidly. Cheyne-Stokes respiration, irrespective of the underlying condition which is responsible for it, is promptly controlled by the administration of small doses, approximately 0.2 gm. given rapidly intravenously just at the beginning of the apneic phase and repeated at a similar point two or three times. That form of dyspnea associated with a sense of oppression but without evidence of circulatory stasis is best relieved by the slow intravenous injection of 0.24 to 0.48 gm. in 10 cc. of distilled water or of 33 per cent glucose solution. Frequently the respiratory distress in cardiac asthma can be much diminished by the same method of administration. The dyspnea of congestive cardiac failure similarly responds very satisfactorily to the injection of a similar dose of metaphyllin combined with salyrgan. Finally, various states of coma such as those associated with narcotic poisoning, cholemia, uremia, etc., are effectively relieved by one or two full doses given intravenously.

Some Actions of Muscle Extract on the Heart Rhythm.—In order to supplement previous observations on the influence of Schwarzmann's extract of skeletal muscle, TURKELTAUB (*Ztschr. f. Kreislaufforschung*, 1931, 23, 601) made electrocardiographic studies upon a group of healthy young men both before and after the subcutaneous injection of 1 cc. of the extract. He noted a moderate degree of slowing of the heart rate without other changes. Where sinus arrhythmia was present before the administration it persisted or was even increased after administration of muscle extract. Premature beats disappeared shortly after the administration of muscle extract, but this effect was only temporary. In patients showing tachycardia due to auricular fibrillation the extract brought about some slowing of the heart rate which had a slight tendency to persist if its administration were repeated daily. However, the previous administration of digitalis to such fibrillating patients seemed to prevent any further slowing due to muscle extract. One patient showing complete auriculoventricular dissociation with occasional premature beats, developed some increase in the frequency of the latter as the result of the administration of muscle extract.

[EDITOR'S NOTE.—While the observations here recorded are suggestive, a study of the cardiograms reproduced shows that in general the changes observed by the author were insignificant in degree and it is questionable, therefore, whether they have any bearing upon the possible therapeutic value of this extract in the conditions studied.]

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Respiratory Failure in Poliomyelitis.—WILSON (*Am. J. Dis. Child.*, 1932, 43, 1433) found that in 6 children suffering from poliomyelitis who had paralysis of the intercostal muscles and the diaphragm without complications such as pneumonia, the Drinker respirator was ideally efficient in maintaining pulmonary ventilation for long periods. A therapeutic trial of the respirator seems desirable as soon as possible after any reduction of the vital capacity is discovered which is due to weakness of the respiratory muscles. Marked dyspnea or cyanosis should not be waited for as indications for the initiation of treatment. The action of the respirator seemed very effective in 2 children with bulbar paralysis without intercostal involvement who had a sudden complete cessation of respiration after choking. The use of the machine seemed sometimes helpful but was often entirely ineffective in 9 children with bulbar paralysis, without intercostal involvement, who had a disturbed central control of respiration, manifested by irregular breathing. Only 2 of these 9 children survived. The use of the machine in cases with bulbar paralysis without intercostal involvement is not recommended except as an emergency and after every attempt has been made to free the pharynx from all secretions. It was not found possible to foretell accurately the effectiveness of the respirator without therapy trial. Except for moderate emphysema found at autopsy, no evidence of harm resulting from the use of the apparatus was found.

A Study of the Water and Mineral Balances in Epileptic Children.—MCQUARRIE, MANCHESTER and HUSTED (*Am. J. Dis. Child.*, 1932, 43, 1519) made intensive studies of the water and mineral balances in the case of a severely epileptic girl under experimental conditions in which changes in the state of hydration of the body have been induced by various procedures, other than water restriction. The establishment of a positive water balance was regularly followed by convulsive seizures, excepting one period when intensive phenobarbital therapy was used. Convulsions, which occurred during two of the periods with slightly negative total water balances, actually followed temporary storage of water. Higher level of water exchange does not necessarily favor the occurrence of convulsions if active diuresis or catharsis prevents water retention. During periods of diuresis when no seizures occurred sodium and chlorin were the predominating minerals of the urine. During the alternating periods of rehydration, when seizures occurred, potassium showed a negative balance with a striking increase in the potassium to sodium ratio. During periods of positive water balance the increase in the potassium to the sodium ratio actually manifested itself from 12 to 36 hours before seizures occurred. This apparent leakage of potassium from the cells, which was most marked during a period of sustained pituitary antidiuresis, may indicate an innate weakness in the retaining membranes, presumably of the cells of the central nervous

system. It is possible that abnormal amounts of water and even sodium found entry to the cells at the same time. The data recorded are tentatively interpreted as favoring the view that an inherent defect in the mechanism for regulating permeability of the brain cell membranes is characteristic of the epileptic state. The specific action of the phenobarbital would appear from the limited data presented to be that of maintaining the normal relationships of the electrolytes and water on the two sides of the cell membrane.

Abortive Poliomyelitis.—PAUL, SALINGER and TRASK (*J. Am. Med. Assn.*, 1932, 98, 2262) made an epidemiologic study of poliomyelitis, in which stress was laid on the problem of so-called abortive poliomyelitis in an effort to define this entity to determine its relative frequency and to bring out methods by which it may be recognized. Common usage of the term abortive poliomyelitis has proved so ambiguous that in order to define the issues in this disease the authors have used the term characteristic minor illness in association with poliomyelitis so that ground may be cleared for a critical, definitive study. The symptomatology of some of these minor illnesses is more or less characteristic but not specific, being essentially that of an acute infection of short duration. Such symptoms as fever, sore throat, headache and vomiting dominate the clinical picture. In a survey of 222 families in each of which 1 or more cases of poliomyelitis had occurred it was found that, coincidentally with the onset of the known case or cases of poliomyelitis, characteristic minor illnesses occurred with a high degree of frequency in the other children of susceptible age. In the age group of 1 to 4 years 39 per cent of children with familial exposure developed a minor illness, and in the age group of 5 to 9 years this incidence was 32 per cent. In 60 control families comparable data were obtained, showing that while the epidemic prevailed, the incidence of similar minor illnesses was about 9 per cent among local children under 10 years of age, who had not been exposed to familial cases of poliomyelitis. In a survey of three communities the ratio of cases of poliomyelitis to these characteristic minor illnesses was in each 1 to 6. Experiments were made in which the poliomyelitic virus was isolated from nasopharyngeal washings in 2 cases of these minor illnesses. Negative results were obtained in 10 others. In both the successful experiments of virus isolation the nasopharyngeal washings were obtained on either the first or the second day of the disease, and three other attempts to isolate the virus during this period proved negative. Strong evidence was developed that these minor illnesses, which are much more frequent than has been suspected, have a common causal relationship with true poliomyelitis.

Vaccine Therapy of Whooping Cough.—WESTENDORFF (*Monatschr. f. Kinderh.*, 1932, 52, 271) tried this treatment in 15 cases. In intervals of from 2 to 3 days he injected increasing doses of a polyvalent gonococcus vaccine, but there was no noticeable change in the course of the disease. Several months later 20 whooping cough patients were treated with a specific whooping cough vaccine. Only in 2 of these children was the whooping cough influenced favorably. In all of the others the treatment was without benefit. In a case of tuberculosis of the bron-

chial lymph glands, in which pertussis vaccine was given as a prophylactic, it developed nevertheless in 2 weeks. In view of other favorable reports in the literature and considering the 2 cases of his own, the author does not feel justified in considering the vaccine therapy as entirely valueless. He considers that it is a distinct disadvantage that whooping cough is not recognized until it is fully developed. Careful consideration of the history, examination of the hemogram and also bacteriologic examination should be helpful in making an earlier diagnosis. If begun in an earlier stage vaccine therapy may be more beneficial.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

The Intracisternal Serum Treatment of Neurosyphilis.—VIEITO (*New Eng. J. Med.*, 1932, 206, 491) believes that the intrathecal administration of serum in cases of neurosyphilis is much superior to the intraspinal method of Swift and Ellis, since the latter not infrequently produces severe pain and sphincteric weakness. The intracisternal serum treatment has produced very favorable and often rapid changes to normal in the spinal fluid findings in a large series of cases studied at the Massachusetts General Hospital and in private practice. The first evidence of improvement is a diminution in the cell count of the spinal fluid, closely followed by a reduction in the amount of protein and a loss of the higher figures in the colloidal gold reaction, which ultimately becomes negative. The Wassermann reaction on the fluid is the last to respond and may be greatly delayed. It may, however, suddenly become negative. A slight rise in any of the figures is an indication for renewal of the treatment. The therapeutic aim is to bring the spinal fluid to normal and keep it so, a result which the author obtained in a large proportion of cases. The method is apparently of no value in cases of optic atrophy, which progresses to blindness despite serologic improvement, and is futile in frank paresis. Cases showing a paretic formula in the spinal fluid but no clinical evidence of the disease, however, should receive the benefit of a trial of this method, which should be abandoned only if no improvement in the spinal fluid occurs after 2 months of treatment. The author believes that the results obtained from intracisternal serum therapy are better than those obtained by other forms of treatment when used in properly selected cases. Frequently as much improvement ensues in the spinal fluid formula in a few months as might be expected in a few years from intravenous therapy. The

treatment should be given not oftener than once every 2 weeks and should be continued until the spinal fluid has approached normal or is in its normal state. The technique is briefly as follows: Fifteen minutes after an intravenous injection of neoarsphenamin 50 cc. of blood are withdrawn into a 150 cc. Erlenmeyer flask and allowed to stand over night at room temperature without agitation. Twelve hours later from, 20 to 25 cc. of serum can be obtained, which is inactivated at 56° C. for $\frac{1}{2}$ hour and then may be kept a number of days to a week in an icebox. It must be warmed to blood temperature before use. If a portion of the serum not used at a single injection is to be used again within the week, it must be inactivated a second time before injection. The Ayer technique of puncturing the cistern is recommended.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Ruptured Endometriomata.—For about 10 years the gynecologic literature has been replete with investigations into the various aspects of endometrial ovarian cysts, or endometriomata, largely due to the interesting and stimulating work of Sampson. While there is still some difference of opinion regarding the exact mode of origin of these cysts, they are sought and identified in many instances in which they were formerly overlooked. One of the complications to which such cysts are liable which has not been generally considered is spontaneous rupture of large cysts. In reporting 3 personal cases and citing another from the literature, NOVAK (*Am. J. Obst. and Gynec.*, 1931, 22, 826) emphasizes the severity of the abdominal symptoms accompanying such rupture. In 2 of his cases the clinical picture was that of acute appendicitis while in the third a diagnosis of twisted ovarian cyst had been made. In the case quoted from the literature the symptoms suggested ectopic pregnancy or acute peritonitis. He believes that this is a rare complication or else is not recognized as these 4 cases are the only ones he has been able to find. However, one of us (F. B. B.) reported a case of this type in 1928 in which the symptoms suggested a perforated duodenal ulcer. At that time a personal communication with Sampson revealed that he had never seen such a condition as here reported. A case closely simulating a ruptured tubal pregnancy has recently been observed (C. C. N.). The possibility of these accidents should be borne in mind when acute abdominal symptoms develop in cases in which the history and pelvic findings suggest the probability of pelvic endometriosis.

Etiology of Ovarian Pregnancy.—A true ovarian pregnancy is of rather rare occurrence and its etiology is not definitely known, but the conception which WOLLNER (*Am. J. Obst. and Gynec.*, 1932, 23, 262) advances is interesting. He believes that in the process of physiologic ovulation, after rupture has taken place, a certain amount of force is required to free the ovum from its attachment to the cumulus oöphorus cells and to expel it from within the follicle. The power of this force depends on two factors. The first is the intrafollicular pressure, and the second is the resistance of the surrounding tissue which in turn is dependent upon the thickness of the membranous wall. Any pathologic alteration which involves the tunica albuginea is likely to produce an increased resistance of the follicle wall and affect the mechanism of ovulation causing the extent of the rupture to be smaller. In this event the liquor will not escape with a sudden gush, but will dribble away slowly, thus not having sufficient momentum to free the ovum and flush it into the abdominal cavity. Such a change in the surface of the ovary is often found in chronic oöphoritis and in such cases the ovary often contains numerous follicle cysts which are nothing but unruptured Graafian follicles, which could not rupture because they met too much resistance in the tunica albuginea. Under the above conditions, although there may be a small rupture, the ovum remains in the ovary, and if it becomes fertilized within the follicle it will develop into an ovarian pregnancy.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

The Importance of Vessel Crossings in the Development of Branch Thrombosis of the Retinal Vein.—According to KÖYANAGI's (*Klin. Monatsbl. f. Augenhcilk.*, 1928, 81, 219) statistics, in 27 cases of branch thrombosis of the retinal veins the superior temporal vein was affected in 22 cases and the inferior temporal vein in 6. No thrombosis of a nasal vein was seen. He believes that the relative frequency of thrombosis in the various venous branches depends on the frequency of arteriovenous crossings in the different quadrants of the retina. Thus, in 124 normal eyes the superior temporal artery and vein were found to cross 194 times, the inferior temporals 80 times, the superior nasals 43 times and the inferior nasals 36 times. Thrombosis always occurs at or peripheral to an arteriovenous crossing. The occurrence of thrombosis at these points is favored by the fact that in many cases, at the crossing, the artery and vein have in part a common wall with closely united adventitia so that changes in the wall or caliber of either artery or vein can narrow the lumen and interfere with the circulation

in the thinner-walled vein. Actual sclerosis of the arterial wall is not a necessary factor. The usual thickening of the arterial wall with increase of elastic tissue which occurs with advancing years may cause sufficient pressure on the vein to initiate a thrombosis. An acute localized inflammatory process in the arterial wall may have the same effect; a venous hyperemia or engorgement may result in thrombosis in the presence of a normal arterial wall. Of the author's 27 patients with branch thrombosis the youngest was 26 years of age, the oldest 84 years and 17 were between the ages of 40 and 60 years; 18 were men and 9 women. In 15 patients the blood pressure was definitely elevated. It was questionably elevated in 4 others. In 8 the Wassermann reaction of the blood was positive. In the early stages of venous thrombosis ophthalmoscopically visible sclerosis in the arterial wall is seldom striking. It is questionable whether the arterial changes demonstrated histologically in the late phases of venous thrombosis are primary or secondary to the disturbance of venous circulation.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DR. WAYNE G. RICHEY, B.S., M.D.,

MERCY HOSPITAL, PITTSBURGH, PA.

A Case of Multiple Papillomata of the Larynx With Aërial Metastases to Lungs.—Theobald Smith once said, "It is the natural history of these (infectious) diseases which we lack." And so it is, in no small measure, with neoplastic diseases. Admitting that, generally speaking, morphology is frequently no index to function, experience has taught us that commonly the clinical course of a given tumor can be predicted quite accurately from its histologic structure. When the methods now at our disposal fail to indicate this parallelism, another—and a very valuable—source of information lies in studying the behavior of the tumor cells, particularly their distribution throughout the body and the relationship they bear to contiguous tissues. Convincing evidence of the value of this latter method lies in a case reported by HIRTZ and OESTERLIN (*Am. J. Path.*, 1932, 8, 333). Over the span of her second year of life an infant developed consecutively a dry irritative cough, gradual loss of voice and a progressive dyspnea which, on direct laryngoscopy was found to be due to, and relieved by removal of, multiple laryngeal papillomas. The tumor proliferated so rapidly that, despite repeated endoscopic interference during the ensuing year a tracheotomy became necessary. Altogether, ten suspension laryngoscopies were done in a 2-year period, at the end of which the little girl died following improper insertion of the tracheotomy tube. Postmortem examination disclosed that the epiglottis was covered and the larynx and the upper half of the trachea were filled with cauliflower-like papillomatous masses. A remarkable condition existed in the lungs, which contained numerous small cavities studded with millet-seed-sized granules. Some of these pulmonary cavities communicated with bronchioles. Small papillary

plugs often occupied the lumina of bronchioli, the columnar epithelial mucosa of which was found sometimes to be intact. When papillomatous masses occurred in alveoli their origin could be traced from bronchioli. Sections from laryngeal, bronchiolar, alveolar and pulmonary tumor tissue showed the same histologic arrangement—a benign papillomatous architecture. No neoplastic cells were found in the lymphatics. The authors regard their case as an actively growing, histologically nonmalignant primary papillomatosis of the larynx. They believe the evidence justifies an interpretation that fragments detached from the laryngeal growth lodged in the bronchioli, where they became implantation metastases, as well as, by virtue of having been aspirated, “aërial metastases” (Letulle).

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Established Actinotherapeutic Modalities in Dermatology.—In the opinion of SCHOLTZ (*Arch. Phys. Ther., X-ray, Rad.*, 1932, 13, 28) the greatest practical problem of scientific physiotherapy is to counteract the flood of commercial literature luring practitioners into physiotherapy by extravagant therapeutic claims. The greatest danger to scientific physiotherapy in dermatology is presented by the mechanistic tendency promoted by the commercial literature, to be satisfied to clear up the individual skin lesions without any attempts of intelligent interpretation of the dermatosis as a whole. This tendency reduces physiotherapeutic clinicians to the level of physiotherapeutic technicians. No physiotherapist is qualified to treat skin lesions unless he has sufficient grounding in dermatologic diagnosis and is competent to administer other dermatologic therapeutic measure if necessary. As a therapeutic weapon in clearing up individual skin lesions, Roentgen ray is much superior to the ultraviolet ray. As a biologic therapeutic agency contributing to the cure of dermatoses, both through systemic and local effects, and from the point of view of general clinical utility to clinical dermatology, the ultraviolet ray is of equal therapeutic value with Roentgen ray and is superior to it in systemic dermatoses. Quartz lamp and carbon arc burners are of identical biochemical and therapeutic capacity and are of equal clinical value. The difference is merely in mechanical and technical details. Full and intense erythema doses of the ultraviolet ray are indicated only in a few types of dermatoses. The majority of therapeutic effects are better obtained with fractional doses. R international units, while physically exact, are not serviceable clinically. McKee's indirect method of measuring Roentgen ray dosage is simple, safe and sufficiently exact for all clinical purposes. Radiologists, as a group, are using in the treatment of skin lesions Roentgen ray of much greater penetration and of a heavier

filtration than is advisable or necessary from a dermatologic point of view. Roentgen ray should be reserved for deep infiltrating dermatoses, granulomata and tumors. Superficial and particularly systemic dermatoses should preferably be treated by ultraviolet ray. The combined and alternate use of fractional doses of Roentgen ray and suberythematous doses of the ultraviolet ray is safe, rational and very effective in a large variety of dermatoses.

Clinical and Roentgenologic Aspects of Ulcerative Colitis.—Ulcerative colitis has been reported from all parts of the world but seems to be more prevalent in the north temperate zone. The disease occurs in every state in the Union. Among predisposing factors, in the opinion of BARGEN and WEBER (*Radiology*, 1931, 17, 1153), are upper respiratory infections and foci of infection in the teeth, tonsils or gall bladder. Much experimental and clinical evidence suggests that a diplostreptococcus closely resembling the pneumococcus, but of characteristic morphologic and biologic properties, plays an important part in the etiology of the disease. Roentgenologic manifestations of the disease, as seen with the barium enema, are characteristic. In about 20 per cent of cases the disease is confined to the rectal segments; the ampulla is markedly narrowed and exhibits a series of coarse linear striations representing barium in the folds of the strongly contracted ampulla. As the disease progresses the ampulla may become narrow, straight and tubular. In a typical, well-advanced case the colon fills to the ileocecal valve almost instantaneously. The colon is shortened and small in caliber; its course is straight and the angles at the flexures approximate right angles. From a soft, pliable, thin-walled, gently winding tube the colon has become a thick-walled, stiff, straight pipe with a small lumen, somewhat analogous in appearance to a thick-walled, tense sclerotic artery. This picture is not easily confounded with that of any other disease of the colon.

A Clinical Evaluation of Various Qualities of Roentgen and Radium Rays for the Treatment of Advanced Cancer.—From his investigation WIDMANN (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 729) concludes that equally good clinical results were obtained with long and short wave length Roentgen and radium rays in a series of epitheliomas of the lip. Skin tolerance is greater for short wave length radiations; there is more penetration but apparently less absorption. Skin tolerance increased when different short wave length radiations were combined, and such combinations are recommended because of the improved clinical results.

Roentgen Ray Treatment of Experimental Tuberculosis.—A number of guinea pigs inoculated with tuberculosis were treated with the Roentgen ray by SPIES (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 716). The progress of the disease was not retarded, and it was indicated, but not proved, that the treatment exerted a deleterious influence. The greater the dosage of organisms the shorter was the subsequent duration of life, but at death the amount of visceral tuberculosis bore no relation to the dosage.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Experimentally Produced Lesions of the Liver.—Studies of experimentally produced lesions in liver were undertaken by BOLLMAN and MANN (*Ann. Int. Med.*, 1931, 5, 699). These authors found that most of the hepatic lesions met with in man could be produced in the experimental animal. Complete removal of the liver results in hypoglycemia with loss of power to form sugar and urea. Amino and uric acids are not destroyed and progressive symptoms of acute hepatic insufficiency with coma, convulsions and death ensue. Partial removal of the organ demonstrated that less than 20 per cent of normal liver substance was sufficient to maintain life. Emphasis is placed upon the great regenerative power of hepatic tissue, partial removal of the organ at repeated intervals showing that the liver is capable of restoration of more than 100 per cent of its weight without signs of hepatic deficiency. This regenerative ability is greatly reduced or absent in obstructive jaundice, in marked cirrhotic changes or where the portal blood supply has been reduced. Ligation of the common duct leads to development of varices, intestinal hemorrhages and ascites. Duodenal ulcer is frequent. Cholecystenterostomy gave rise to a low-grade infection of biliary ducts with production of an infective type of cirrhosis. Repeated administration of carbon tetrachlorid and tetrachlorethane produced a picture resembling portal cirrhosis; with more extensive injury a subacute yellow atrophy is produced. Alcohol greatly increased the toxicity of several toxic substances. Signs and symptoms of hepatic insufficiency only supervene when the organ has suffered very profound alterations, most of the liver function tests failing to show any pathologic change until this has occurred. Satisfactory correlation between the amount of liver damage and the degree of retention of bromsulphthalein was usually, although not invariably, found. The ascites which occurs spontaneously in extensive experimental cirrhosis and obstructive jaundice of long duration may be produced by feeding the animal meat or meat extractives. The disappearance of ascites, which occurs when these substances are withdrawn is facilitated by large amounts of carbohydrate. Salt appears to play no part in the production of ascites and the great protective value of carbohydrate against hepatic injury is emphasized.

Tumors of the Islands of Langerhans and Hypoglycemia.—Five cases of tumors of the islands of Langerhans have been reported by SMITH and SIEBEL (*Am. J. Path.*, 1931, 7, 723). Four of these cases were observed at autopsy while in 1 the tumor had been successfully removed by surgical operation. Two of the cases presented a definite history of hypoglycemia, 1 a questionnaire history, 1 had no symptoms

referable to the pancreas and in 1 a mild diabetes was present. The authors consider all their cases as adenomas rather than carcinomas or hypertrophied islet tissue. In some of the tumors the cells contain abnormal secretory granules while in others they are absent. It is believed that tumors producing hypoglycemia are composed largely of beta cells. In the authors' cases the islets in the remainder of the pancreas are of normal size and show a normal granular content. The activity of the normal islets does not seem to have been depressed by the excess of insulin produced in the tumor. The latter is not controlled by the normal mechanism governing insulin production and may produce hypoglycemia even when small. The occurrence of mild diabetes in 1 case suggests that the low sugar tolerance is dependent upon some developmental defect of the islets which also is responsible for the growth of the adenoma.

On the Structural Changes of the Tunicæ in Varicose Veins.—From a study of tissue removed at operation MAGGIO (*Lo Sperimentale*, 1931, 85, 185) concludes that varices occurring in the saphenous vein and pampiniform plexus may show two distinct types of lesions. In the first there is primarily degeneration of the muscle fibers of the media. Accompanying this is an irregular compensating increase in the elastic fibers and laying down of connective tissue in the middle and outer coats; this causes distortion and often narrowing of the lumen of the vessel. This newly formed tissue is also liable to undergo hyalin degeneration, so that when stasis is superimposed thinning of the wall and irregular dilatation take place. The intima plays very little part in the process, although in the advanced stages the whole vessel wall is transformed into a more or less clear substance, showing no semblance of cellular structure. In the second type it is the intima which is the seat of the initial lesion. An overgrowth of the subendothelial connective tissue in a diffuse or patchy manner and splitting of the internal elastic lamina into many layers causes narrowing of the lumen. As time goes on the elastic tissue of the media increases and also tends to invade the adventitia. Finally, the new tissue in all three layers degenerates, so that there are left areas of a thin, hyalin material, interspersed with portions in which the process is still active. Both varieties of change are considered to be caused by a toxic process, possibly associated with deranged endocrine function.

The Morbid Anatomy of the Diaphragm.—A study of the morbid anatomy of the diaphragm has been made by LUCKÉ (*Ann. Int. Med.*, 1931, 5, 750) and a series of 164 cases has been reviewed. In this series carcinoma occurred in 14 cases, sarcoma in 3 and hypernephroma in 1. Carcinoma of the diaphragm, most often arising primarily in stomach, spreads throughout the muscle bundles from the subserous lymphatic channels, giving rise to a diffuse flat nodular infiltration with usually a considerable destruction of tissue. Tuberculosis, which was present in 35 cases, most frequently occurred as a serositis but also as isolated or conglomerate tubercles. The peritoneal surface was more often involved, even when the primary focus was above the diaphragm; adhesions to adjacent organs were common and much destruction of muscle sometimes occurred. Acute diaphragmitis was present in 25

cases with inflammation of both serous surfaces and in each case involvement of the muscle in either a degenerative or inflammatory process. The latter which most commonly was associated with pneumonia presented a picture of a true myositis with edema, polymorphonuclear infiltration and the formation of fibrin, later going on to organization and scar formation leading to inference of muscular contraction. Hydropic degeneration and Zenker's hyalin degeneration were frequently seen and cloudy swelling and fatty degeneration often occurred. The author believes that these processes commonly occurring in pneumonia may play an important part in bringing about respiratory failure in that disease.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Scarlet Fever Streptococcus Antitoxin in the Treatment of Scarlet Fever.—VELDEE, STEVENSON and MITCHELL (*Pub. Health Rep.*, 1931, 46, 3023) made a most carefully controlled study of the therapeutic value of two samples of scarlet fever antitoxin. The discussion which gives briefly the results of the work is as follows: We have attempted to present in this report a detailed analysis of each case included within our study, the purpose being not only to note the more obvious clinical variations in our three groups but also to analyze the records more minutely with a view to determining wherein, if at all, scarlet fever streptococcus antitoxin fails to accomplish its purpose. That the antitoxin has a specific neutralizing effect on the toxin *in vivo* is indicated by the decrease in the duration of the rash, by a change in the character and extent of the desquamation, and by a reduction in the number of complications. That it failed to neutralize completely the damaging effect of the toxic substances produced by the scarlet fever infection is suggested by the failure of the rash to disappear promptly, by the continuation of the fever and by the appearance of complications in a certain number of serum-treated cases. These failures may have been caused by (a) too small a therapeutic dose, (b) an improper method of administration, (c) administration too late in the disease, or (d) an inadequacy of antitoxin to neutralize all of the toxic substances elaborated in this disease. It is our belief, and this is confirmed by other clinicians and by investigations of the action of scarlet fever toxin, that early administration of antitoxin and its rapid dissemination throughout the body of the patient are essential; the toxin being elaborated very early in the disease and effecting its tissue damage without delay. The probability of serum sickness must also be weighed in the use of scarlet

fever antitoxin. However, the frequency of this complication cannot be attributed entirely to a peculiar property of an antistreptococcic serum itself, since it was shown that previous sensitization to horse serum played an important rôle in its incidence. With the introduction of a more effective method of producing active immunity against diphtheria by the use of toxoid instead of toxin-antitoxin mixture, there will be a corresponding reduction in the percentage of children sensitized to horse serum. There is also the fervent hope that ultimately an improved method of manufacture will become available so that the volume of the therapeutic dose of scarlet fever streptococcus antitoxin may be greatly reduced, which in itself will minimize the probability of serum sickness.

Changes in Ionic Content of Air in Occupied Rooms Ventilated by Natural and by Mechanical Methods.—Intensive investigations have until now failed to discover the specific cause of deadness, or lack of a stimulating quality, in the air of occupied rooms, even when temperature and humidity are controlled, as contrasted with the air of the open country. Proponents of the open air treatment ascribe this quality of freshness to a vital principle which is lost when air is brought indoors, particularly when ventilation is effected by mechanical means. In recent years, since the carbon dioxid, oxygen and crowd poison theories have become obsolete, ionization has been suggested as the air-soluble vitamin, but it has not yet been identified. The virtues of artificially ionized air have been extolled on purely theoretical grounds, with no scientific confirmation whatever. YAGLOU, BENJAMIN and CHOATE (*J. Soc. Heating, Piping and Air Conditioning*, October, 1931, p. 865) have studied the problem of ionization in relation to ventilation and health. Their paper deals largely with fundamental changes in the ionic condition of the air in occupied rooms ventilated by natural and by mechanical methods, and with the influence of various air conditioning processes upon the ionic content of air. A series of experiments was carried out in rooms, both occupied and unoccupied: (1) With no ventilation; (2) with window-gravity ventilation; (3) with mechanical ventilation, in order to determine the extent to which the number of small ions is affected by respiration and transpiration and by modern air-conditioning methods. In contract with the prevailing belief, the ionic content in unoccupied heated rooms did not differ much from that out of doors, and in cold weather it was often higher, owing probably to a temperature effect. In occupied rooms there was a marked decrease in both positive and negative ions. Immediately after the occupants assembled the ionic content of the air fell abruptly to a very low value, which was maintained until the occupants left the room. Both positive and negative ions began to rise again as soon as the people departed. The minimum supply of outdoor air required to maintain normal ionic content in a crowded room was found to be prohibitively high (160 cfm. per person). With the usual air supply of 30 cfm. per person, the ionic content did not seem to differ greatly from that with no ventilation at all. On the other hand, it was possible by means of artificial ionization to control both the quantity and the quality of ions at any desired concentration up to 10,000 ions per cubic centimeter, with or without ventilation. Mechanical ventilation reduced the ionic content from

0 to 30 per cent by diffusion and adsorption to metal conductors. Heating the air by means of a central fan system increased the ionic content, and cooling by similar methods decreased it. The usual method of washing humidifying or dehumidifying by means of water sprays, deprived the air of all small ions, and produced a great number of large negative ions, or condensation nuclei, by the well-known Lenard effect. Recirculation reduced both positive and negative ions by diffusion and adsorption to metal conductors.

Antitoxin Immunity to Diphtheria in Relation to Tonsillectomy.—WHEELER, DOULL and FROST (*Am. J. Hyg.*, 1931, 14, 555) state that the conditions of observation in the two Baltimore groups, of school-children and students, respectively, are not entirely comparable to those obtaining in the most significant of the groups studied by Schick and Topper. The latter cite observations on children known to have been Schick-positive immediately before tonsillectomy and retested usually within 6 months thereafter, while the Baltimore records for children who have undergone tonsillectomy refer to Schick tests performed some years after the operation. Hence, a possible explanation of the discrepancy between the results is that the negative reactions which Schick and Topper found developing so commonly and quickly after tonsillectomy may have been temporary, tending to revert within a few years to positive reactions. This explanation does not seem probable, for although reversions from Schick-negative to Schick-positive reactions are not very uncommon, all the evidence at present available indicates that in any considerable group of children under natural conditions, the tendency is regularly toward a progressive increase, year by year, in the proportion of negative reactors. Therefore, if tonsillectomy in the groups observed in Baltimore had tended to stimulate the development of antitoxic immunity at anything like the rate indicated by Schick and Topper's observations, one would expect that the effect would still be clearly demonstrable after the lapse of several years. In view of this wide divergence, the need for further observations on the subject is obvious.

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ORIGINAL ARTICLES.

THE HEART IN FUNNEL CHEST.

By JOSEPH EDEIKEN, M.D.,

AND

CHARLES C. WOLFERTH, M.D.,

PHILADELPHIA.

(From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.)

FUNNEL chest (pectus excavatum, Trichterbrust) is characterized by a depression of the lower end of the sternum. It was first described by Bauhinus¹ in 1594. It was again mentioned in an anonymous note² in 1860, and in March of the same year Woillez³ described the case of Heinrich Wojaczek, a young Viennese medical student. Thereafter occasional reports on isolated or comparatively small groups of cases appeared, and in 1909 an exhaustive study of the literature was made by Eric Ebstein.⁴ Although he collected 97 previously reported cases, his work was essentially a discussion of the various theories of the etiology of trichterbrust and was incomplete from the clinical point of view.

The deformity varies considerably in size and depth—from a very slight depression to one in which the entire sternum is involved. The deformity of Woillez's patient was considerable, measuring 25 cm. in the vertical diameter, 18 cm. transversely and 7 cm. in depth. In his case Woillez estimated the distance between the anterior surface of the spine and posterior surface of sternum at its deepest part to be but 1 cm. Although mild cases of funnel chest are common, the moderate and severe forms are infrequent, but not as uncommon as the meager literature would lead us to

believe. Eichhorst⁵ found 6 cases among 14,000 patients and Rosenfeld⁶ found 4 cases among 4386 deformities of various types. We have been able to assemble 10 cases of moderate or severe degree (Table 1) in a comparatively short time. Three cases were referred by an orthopedic surgeon, 2 by two medical colleagues and the remaining 5 cases were seen in private practice.*

Most cases of funnel breast are either congenital or acquired in early life; a third class is definitely traumatic in origin. The congenital type has been ascribed to various causes. Eggel⁷ believed it due to a nutritional disturbance, causing a softening of the sternum which permits it to be depressed by atmospheric pressure. Langer and Zuckerkandl,⁸ and Ribbert,⁹ pointed out the possibility of extrauterine pressure as the cause. Von Heuter and Niemeyer¹⁰ considered it a manifestation of fetal rickets. Syphilis was thought to be the etiologic factor by Gaucher.¹¹ W. Ebstein¹² believed it due to an embryologic defect or arrest of development of the sternum. Flesch¹³ ascribed it to an abnormal length of the ribs. The acquired type has been ascribed to rickets,¹⁴ obstruction to respiration because of adenoids and asthma,^{15,16,17} faulty posture,¹⁸ mediastinal adhesions.¹⁹ Déjerine²⁰ has seen it in association with progressive muscular paralysis. While it is not within the province of this paper to discuss the various theories proposed to explain this deformity, it is agreed that the congenital cases are developmental and the changes in position of the heart and other viscera described below have been found in infants at birth.^{1,21,22} In most of the acquired cases the deformity which is small and usually noted at an early age¹⁸ increases in size with the growth of the thorax.

Signs and Symptoms. Because the excavation usually involves the region of the precordium, the thought presents itself that serious cardiac disturbance might readily occur. However, among the uncomplicated congenital cases, comparatively few complaints of cardiac symptoms have been noted irrespective of the size of the depression. (Table 1.) Sauerbruch has reported 2 cases having only mild funnel chest deformity associated with cardiac symptoms, but such cases are apparently exceptional. The tremendous deformity of Woillez's case was discovered during routine examination, for the young man, 23 years of age, was in excellent health and had never complained of cardiac or pulmonary symptoms. It is also interesting to note that this same Heinrich Wojacek exhibited himself before the various European clinics for many years. Our oldest patient, I. C. (Table 1; Fig. 1), was 69 years of age and was symptom-free and had never any serious cardiac or pulmonary disorder, although his deformity measured 10 cm. in transverse diameter, 9½ cm. in vertical diameter and was 5 cm. deep. Judson's²¹

* We wish to express our thanks to Dr. A. M. Rechtman, Dr. J. Q. Griffith, Jr., and Dr. Sloan Stewart for referring the above cases.

TABLE 1.—DATA ON 10 CASES OF FUNNEL CHEST.

No.	Initials.	Sex.	Age years.	Etiol- ogy.	Dura- tion.	Depth of depression.	Ext. depth of chest.		Inter. diam. of chest.		Heart diam.		Index.	E.K.G.	Cardiovascu- lar symptoms.	Exercise toler- ance.	Complication.
							At de- formity.	Above.	Trans- verse.	A.P.	Trans- verse.	A.P.					
1	C. Y.	M.	7 mos.	Cong.	7 mos.	1.5 cm.	8.0	9.5	Not meas.	..	Not meas.	Normal	None		
2	J. C.	M.	9	Cong.	9 yrs.	2.0	9.3	12.2	18.4	6.0	10.0	5.4	5.40	Normal	None	Good	None.
3	M. W.	M.	11	Cong.	10 yrs.	3.0	9.5	12.5	20.0	7.0	10.3	5.5	5.34	Normal	None	Good	None.
4	J. A.	M.	14	Acq.	10 yrs.	3.5	15.5	19.0	19.3	10.5	Normal	None	Good	None.
5	M. W.	M.	17	Acq.	5 yrs.	3.0	13.0	16.0	24.7	7.2	10.5	6.8	6.48	Normal	None	Good	None.
6	W. A.	M.	19	Acq.	9 yrs.	2.0	17.0	19.0	21.6	14.0	13.0	9.8	7.54	Q-R-S split	Dyspnea, cya- nosis, edema of ankles	Poor	Kyphoscoliosis; pigeon breast.
7	J. C. H.	F.	22	Not known	Not known	Not measured; moderate	25.1	..	12.0	6.2	5.20	Normal	Severe attacks of precordial pain	Fair	Hist. of rheum. fever and peri- carditis at 8 yrs.; moderate scoliosis.
8	W. L.	M.	33	Cong.	33 yrs.	Not measured; extreme	Paroxysms of aur. fibril.	Parox. aur. fi- bril. for 8 yrs.	Good	None.
9	N. W. P.	M.	34	Acq.	22 yrs.	4.0	14.0	18.0	25.0	7.0	12.7	7.9	6.20	Prolonged P-R interval	Low blood pres- sure; weak	Good	Myocardial disease?
10	I. C.	M.	69	Cong.	69 yrs.	5.0	15.0	20.0	26.4	7.8	12.0	7.9	6.60	Q-R-S com- plexes split and widened; left axis devia- tion	None	Fair	None.

patient, a man, aged 71 years, also was symptom-free. It is difficult to conceive of the heart being so markedly displaced and flattened as in Fig. 2 without showing evidence of cardiac dysfunction, but the slow development in the congenital and most of the acquired cases probably allows for accommodation not only within the chest but also within the heart.

In the vast majority of cases the deformity is noted at birth or in early childhood and is comparatively small. Occurring at a time when the organs have the greatest power of adaptation and long before the growth of the thorax is complete, the narrow antero-posterior diameter of the chest is compensated by an increased growth in breadth of the chest; the heart, mechanically impeded in its growth by the depression, compensates by a comparatively greater increase in its transverse diameter. None of our cases showed an undue twist or kink of the aorta, the slow development probably allowing for compensation.

Rapid formation of the depression, as seen in traumatic cases, does not allow for this accommodation and, according to the literature, symptoms, especially pain and dyspnea, are usually present. Alexander²⁵ recently reported 2 cases of traumatic funnel breast. Pain and dyspnea, which were prominent symptoms in both cases, were relieved by operation.

It is difficult to evaluate the symptomatic effect of funnel breast upon those cases complicated by a spinal deformity and those associated with organic diseases of the heart. We shall show in a future paper that spinal deformities, especially scoliosis and kyphoscoliosis, exert a profound influence upon the size, shape, position and functional capacity of the heart. The chest is distorted and the lung on the side of the deformity is compressed while the opposite lung shows a compensatory emphysema. Furthermore the chest is fixed and does not allow proper ventilation of the lungs; the chest is often small, for the deformity is usually complete before bodily growth and therefore lags somewhat behind. In some cases the pulmonary artery is found kinked and twisted at postmortem. The above factors all throw an added load upon the right heart. As a result signs and symptoms referable to weakness of the right heart appear early. Our patient (Fig. 3) complained of dyspnea, edema of the legs and was somewhat cyanotic. Although there was a moderate funnel chest, the kyphoscoliosis is compensated for by the depression. Since the heart was not compressed, the funnel chest probably did not play any part in the production of his symptoms.

Another patient, a draftsman, first observed the depression at the age of 12 years and was well until he was 34 years, when he developed weakness and low blood pressure. At preparatory school he was a cross-country runner and played ice hockey, basketball and tennis. During the World War he was in the navy and at no time experienced any symptoms referable to the cardiovascular

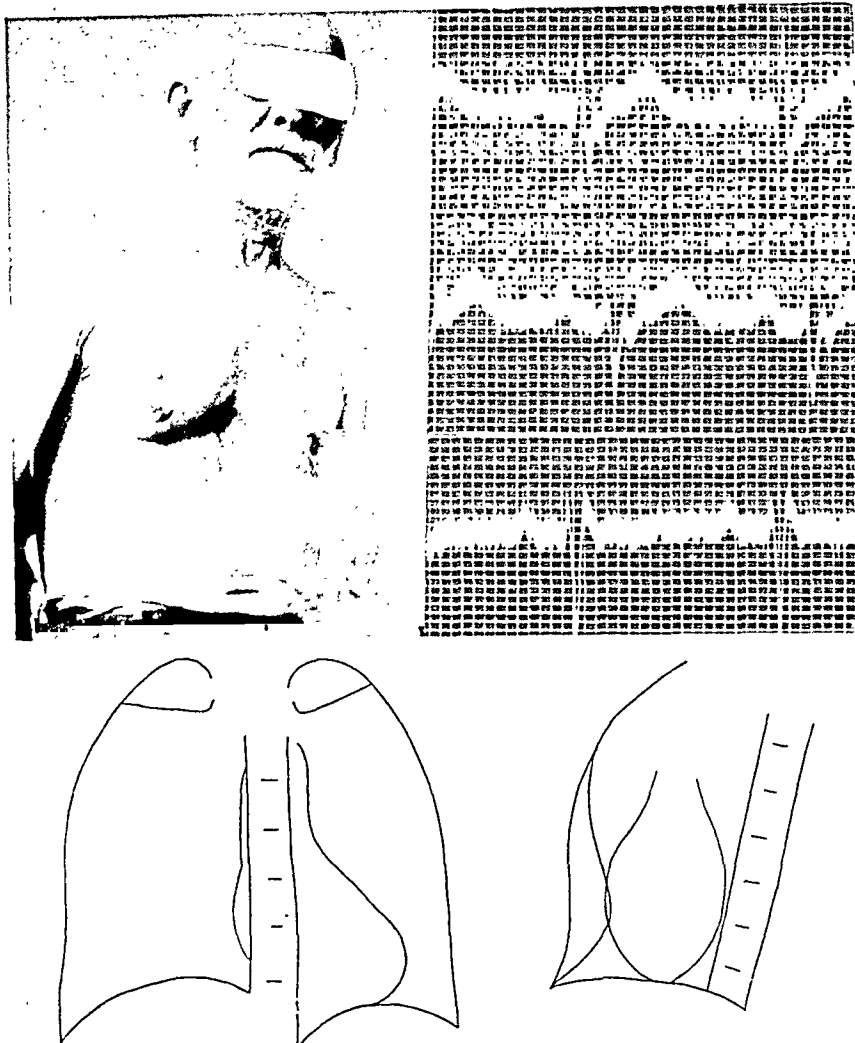


FIG. 1.—Case 10. Congenital funnel chest in man, aged 69 years. In lateral view note the clear space in front of heart, the anterior border of which is formed by the chest wall, the posterior by the depressed sternum. The heart is displaced to the left and slightly upward and because of the asymmetry of the depression, its anterior border is seen in front of the shadow of the sternum.

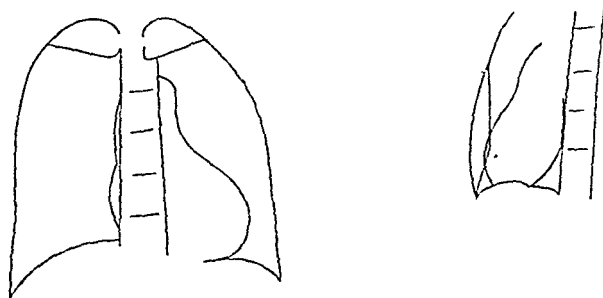
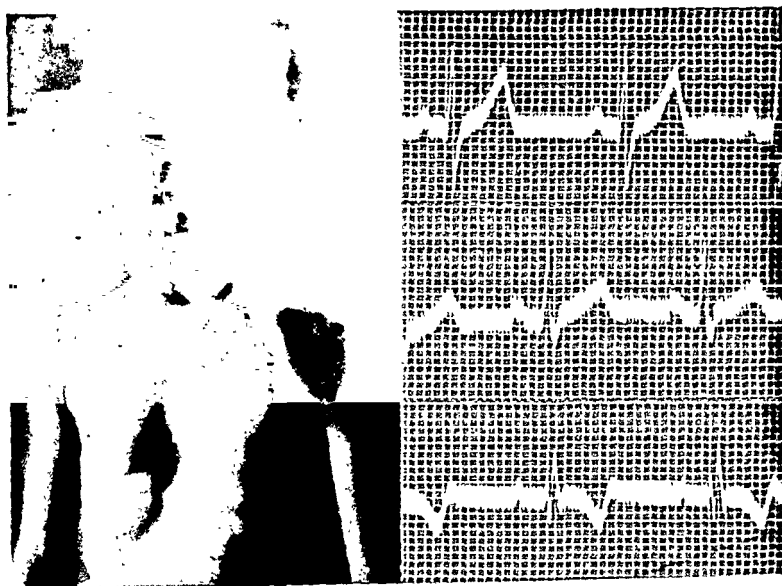


FIG. 2.—Case 3. Congenital funnel chest in boy, aged 11 years. The heart is markedly flattened in the anteroposterior diameter and is displaced to the left and slightly upward.

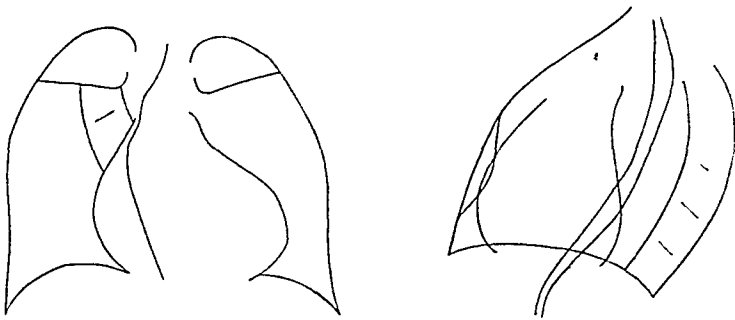
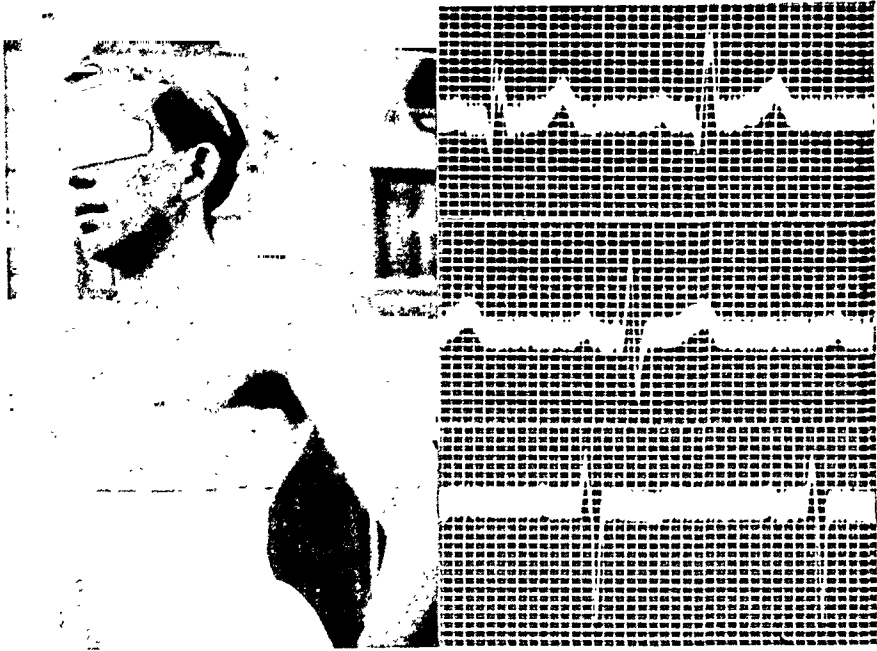


FIG. 3.—Case 6. Acquired funnel chest in young man, aged 19 years, complicated by a kyphoscoliosis and pigeon breast. The heart is not displaced or flattened. Note the scoliotic spine to the right of the heart. The esophagus is seen behind the heart.

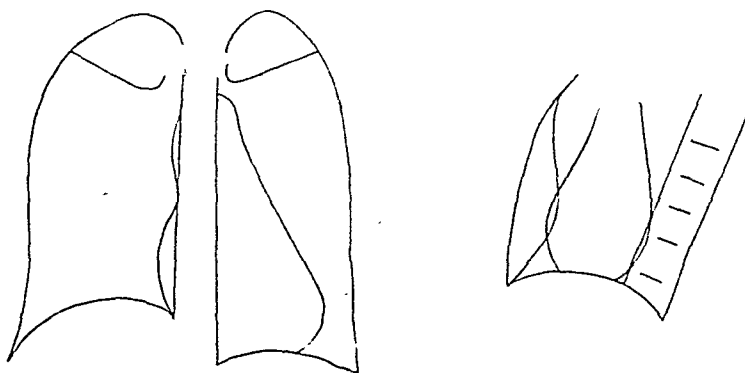
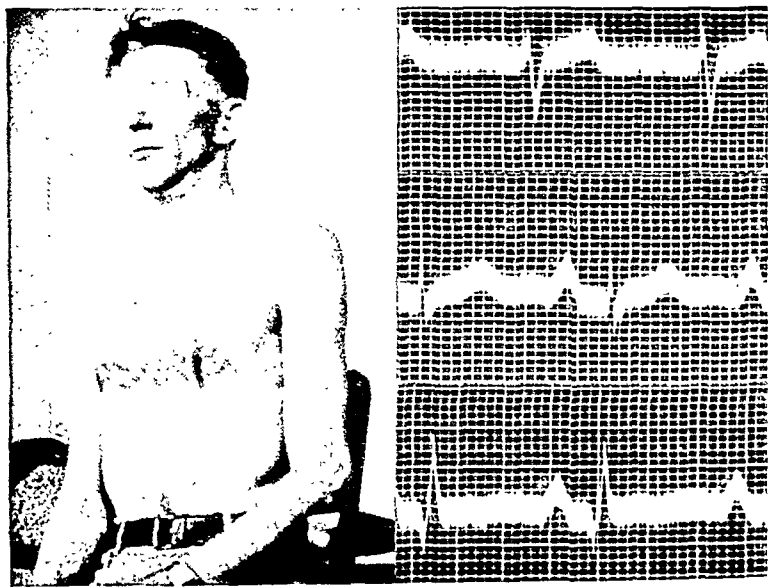


FIG. 4.—Case 9. Acquired funnel chest in man, aged 34 years. The depression is primarily left side. Note the "mitralization" of the heart, probably the result of rotation by the left-sided depression.

system. Although it is impossible to state with certainty what effect his funnel depression had upon his present condition, it is improbable that a condition which apparently did not affect his cardiovascular system during his strenuous athletic career would affect it seriously during a period of comparative inactivity. The depression in this case has the uncommon feature of being primarily left-sided. Fluoroscopically, the heart appeared rotated to the right by the left-sided depression, and this probably accounts for the "mitralization" (Fig. 4) and the right axis deviation observed in the electrocardiogram. (Fig. 4.)

Sauerbruch²³ reported a case of paroxysmal fibrillation in an uncomplicated funnel chest which cleared up after operation. Paroxysmal fibrillation has occurred in 1 of our cases (W. L.) on a number of occasions during the past 7 years and, although the deformity might have been a predisposing etiologic factor, all the attacks have apparently been precipitated by gastrointestinal upsets. The cardiac rhythm in all other cases has been normal.

Because of the deformity, the right border of the heart is difficult to determine by percussion, but the apex is usually found to the left of the midclavicular line, occasionally as far as the axillary line. Pericardial friction sounds have been described by Smith²⁶ but were not elicited in any of our cases. In Case 7, however, there is a history of rheumatic pericarditis in childhood. Systolic murmurs were heard in 5 of our cases. Four were soft, blowing, not transmitted and no special significance could be ascribed to them. One (Case 9) was heard in the region of the tricuspid valve, but only in the upright position. It was rather rough, markedly influenced by respiration and disappeared immediately when the recumbent position was assumed.

Responses to exercise tolerance tests were good in all the uncomplicated cases except in Case 10. Although the heart rate remained somewhat accelerated and there was some dyspnea on exertion, one is scarcely justified in ascribing these reactions to congenital funnel breast in a man aged 69 years.

German authors^{1,12} consider patients with funnel chest susceptible to pulmonary complications, especially bronchitis and tuberculosis. In this country Shively²⁷ reported 17 cases of funnel chest, and of these 10 had active tuberculosis. However, all his cases were seen in tuberculosis sanatoria. None of our cases gave a history of frequent colds or pulmonary disorder nor was there any evidence of active tuberculosis found on clinical examination.

Fluoroscopic Examination. The heart in cases with moderate or severe deformity tends to be displaced to the left and usually upward, the amount of displacement depending upon the size, shape and position of the deformity. In severe cases the apex may reach the anterior axillary line, but in mild cases little if any displacement is observed. (Fig. 4.) Pericardial and mediastinal

adhesions²⁸ may prevent displacement of the heart or cause it to be drawn to the right. Case 7 failed to show any displacement, and because of the history of pericarditis in childhood adhesions were considered as a possible explanation. Occasionally the deformity is preponderatingly left-sided rather than nearly symmetrical, and under these circumstances the heart is either displaced or rotated to the right. (Fig. 4.) Usually, however, the right border of the heart is close to or lost within the shadow of the spine. The under surface of the heart can be seen to an unusual extent and in some cases it is raised from the diaphragm so that in inspiration a clear space is seen between the two. The heart appears somewhat larger than normal, but unlike hypertrophied hearts, which are denser than normal, appears more transparent. The lateral view shows the heart and chest to be extremely narrow, which would account for its unusual transparency in the anteroposterior view. Rösler,²⁹ in a study of normal hearts, found the ratio of the anteroposterior to the transverse diameter to be about 0.7 to 1. In funnel chest this ratio is often reduced to 0.5 to 1, or less. Instead of the sternum forming the anterior chest border there is a large air-containing space formed by the bulging right and left chest. Behind this the deformed sternum can be seen. Occasionally, because of the asymmetry of the depression, the heart can be seen pulsating in front of the plane of the sternum.

Electrocardiographic Study. The electrocardiograms showed no definite abnormalities which could be attributed to the funnel depression. The one of the aged individual showed a left axis deviation and evidence pointing to depression of myocardial function, but in a person aged 69 years these changes cannot be ascribed to a funnel depression.

Case 9 showed a conduction defect (*P-R* interval, 0.24 second) but this cannot be attributed to the funnel depression. The right axis deviation observed in this case may have resulted from rotation of the heart produced by a primarily left-sided funnel depression.

The electrocardiograms of the other 7 uncomplicated cases were normal, and did not show axis deviation, probably because the heart as a whole was displaced upward and to the left without rotation of its electrical or anatomical axis.

Summary. Ten cases of moderate or severe funnel chest were studied in order to determine its effect upon the heart. There were 9 males and 1 female. The ages ranged from 7 months to 69 years. The deformity was probably acquired in 4 cases, in 5 congenital and in 1 unknown. One case was complicated by a kyphoscoliosis and pigeon breast. Clinically the latter was the only one who showed evidence of cardiac decompensation, but it is believed this was due to the lung lesions resulting from the spinal deformity. Electrocardiograms were normal in 7 uncomplicated cases. Two cases showed evidence of depressed myocardial function. Fluoro-

scopically the heart was flattened in the anteroposterior diameter and correspondingly enlarged in the anteroposterior view; it was displaced upward and to the left, and in 1 case appeared rotated to the right.

Conclusions. 1. Funnel chests of moderate and severe grades are not as uncommon as the meager literature would lead one to believe. Mild degrees of funnel chest are common.

2. Funnel chest of moderate or severe grades causes a displacement of the heart to the left and usually upward. The heart is enlarged in its transverse diameter, but the anteroposterior diameter is decreased. Occasionally the heart is rotated by a marked asymmetrical depression.

3. Although the heart is displaced, electrocardiograms fail to reveal any consistent deviation of the electrical axis, probably because the heart is displaced as a whole.

4. Uncomplicated funnel chest does not appear to have any clearly defined effect upon the functional capacity of the heart unless the deformity is traumatic or of rapid development.

5. The lack of symptoms can probably be explained by the slow development in the vast majority of cases. This allows for accommodation within the chest and heart.

BIBLIOGRAPHY.

1. Herrmannsdorfer, A.: *Handb. d. prakt. Chir.*, 6th ed., 1930, 2, 15.
2. Anonymous: *Difformité thoreaque*, *Gaz. d. hôp.*, January 7, 1860, vol. 10.
3. Woillez: *Sur un cas de difformité thoracique considérable*, *Union méd.*, 1860, 2, 515.
4. Ebstein, E.: *Ueber die angeborene und erworbene Trichterbrust*, *Samml. klin. Vortr.*, 1909-1910, 167-196, 1-38.
5. Eichhorst, H.: *Erworbene Trichterbrust*, *Deutsch. Arch. f. klin. Med.*, 1891, 48, 613.
6. Rosenfeld, L.: *Zur Statistik der Deformitäten*, *Ztschr. f. orthop. Chir.*, 1902, 10, 405.
7. Eggel: *Eine seltene Missbildung des Thorax*, *Virchow's Arch. f. path. Anat.*, 1870, 49, 230.
8. Langer and Zuckerkandl, E.: *Untersuchungen über den missbildeten Brustkorb des Herrn J. W.*, *Allg. Wien. med. Zeitung*, 1880, 49, 514.
9. Ribbert, H.: *Zur Aetiologie der Trichterbrust*, *Deutsch. med. Wehnschr.*, 1884, 10, 533.
10. Von Heuter and Niemeyer, quoted by Shively: *Am. Med.*, 1912, 18, 26.
11. Gaucher, E.: *Thorax en entonnair et hérédosyphilis*, *Semaine méd.*, 1901, 21, 359.
12. Ebstein, W.: *Ueber die Trichterbrust*, *Deutsch. Arch. f. klin. Med.*, 1882, 30, 411.
13. Flesch, M.: *Ueber eine seltene Missbildung des Thorax*, *Arch. f. path. Anat.*, 1873, 57, 289.
14. Steindler, A.: *Diseases and Deformities of the Spine and Thorax*, St. Louis, C. V. Mosby Company, 1929, p. 81.
15. Codman, C. A. E.: *Proc. Philadelphia Med. Soc.*, 1901, 22, 132.
16. Van den Bergh, A. A. H.: *Over een Borst-Misvorming*, *Nederl. Tijdschr. v. Geneesk.*, 1919, 2, 1245.
17. Osler, W., and McCrae, T.: *Principles and Practice of Medicine*, 11th ed., New York, D. Appleton & Co., 1930, p. 467.
18. Kuhns, J. G.: *Funnel Chest Deformity*, *New England J. Med.*, 1931, 204, 1077.

19. Raubitschek, F.: Zur Kasuistik der Trichterbrust, Arch. f. Orthop., 1905-1906, 4, 86.
20. Déjerine, J.: Sur la deformation de la cage thoracique dans certaines atrophies musculaires, Compt. rend. Soc. de biol., 1891, 9, 50S.
21. Bein, G.: Zur Anatomie und Aetiologie der Trichterbrust, Zieglers Beitr. z. path. Anat., 1912, 52, 567.
22. Frühwald, H. E.: Zwei Fälle von kongenitaler Trichterbrust, Zieglers Beitr. z. path. Anat., 1913, 56, 13.
23. Sauerbruch, F.: Chirurgie der Brustorgane, Berlin, 1920, 1, 440.
24. Judson: Funnel Chest, Med. News, 1901, 78, 644.
25. Alexander, J.: Traumatic Pectus Excavatum, Ann. Surg., 1931, 93, 489.
26. Smith, K. S.: The Heart in Thoracic Deformity, Middlesex Hosp. J., 1930, 30, 43.
27. Shively, H. L.: Funnel Breast Deformity Considered Especially in Its Relation to Tuberculosis of the Lungs and Other Diseases of the Chest, Am. Med., 1912, 18, 26.
28. Pohl, R.: Trichterbrust und Herzform, Wien. klin. Wchnschr., 1928, 41, 1439.
29. Rösler, H.: Zur röntgenologischen Beurteilung des Herzgefäßbildes bei Thoraxdeformitäten, Deutsch. Arch. f. klin. Med., 1929, 164, 365.

GROSS CARDIAC HYPERTROPHY IN MYOCARDIAL INFARCTION.*

BY ELMER C. BARTELS, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,
ROCHESTER, MINNESOTA,

AND

HARRY L. SMITH, M.D.,

ASSOCIATE IN SECTION IN DIVISION OF MEDICINE, THE MAYO CLINIC, AND INSTRUCTOR IN
MEDICINE, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

THERE seems to be considerable disagreement in the literature as to whether severe coronary disease and cardiac infarction do or do not produce cardiac hypertrophy. We recently reported 2 cases of cardiac infarction affecting young persons, in which there was marked gross cardiac hypertrophy. The impression given in the literature, and these 2 striking cases, prompted us to make this study, which consisted of a review of 8912 records of necropsy. Out of this number of records of postmortem examination, we obtained 42 in which there was evidence that the coronary arteries had been diseased sufficiently to produce definite chronic infarction.

In selecting this material we excluded all cases in which there was any condition that is known or is supposed to produce cardiac hypertrophy. We excluded all cases in which there was hypertension or a history of blood pressure of more than 150 mm. of mercury systolic, and 90 diastolic. That is, we took a reading of 150 systolic and 90 diastolic for our upper limit of normal. There were 9 of these cases that had been observed over a period of several

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years. Some of the patients had had only one reading of blood pressure, and of course we cannot be absolutely sure that some of them had not had hypertension in the past, although when they

TABLE 1.—SUMMARY OF CARDIAC WEIGHT OF PATIENTS WITH MYOCARDIAL INFARCTION.*

I	II	III	IV	V	VI	VII	VIII
Case.	Age, years.	Body weight, pounds.	Cardiac weight, gm.	Calculated normal cardiac weight, gm.	Cardiac weight, +8 per cent for error.	Increase.	
						Percentage (column VIII minus column VI).	Grams (column IV minus column VI).
1	35	183	715	357	385	85	330
2	36	141	540	275	297	81	243
3	41	185	368	361	381		
4	46	200	600	390	421	42	179
5	47	120	385	234	251	54	134
6	48	161	475	314	339	40	136
7	50	163	275	318	343		
8	50	170	460	332	358	28	128
9	51	160	650	309	333	95	341
10	52	200	487	387	411	18	76
11	55	145	466	283	315	47	151
12	54	154	411	301	325	26	86
13	54	153	486	296	319	52	190
14	54	120	332	234	252	31	80
15	54	198	355	387	418		
16	55	168	388	328	354	9	34
17	56	135	480	263	284	68	196
18	56	125	338	240	259	30	79
19	56	170	400	331	357	12	43
20	57	181	520	353	381	36	239
21	57	140	475	273	294	61	181
22	59	150	425	293	316	34	109
23	59	166	580	322	347	38	233
24	59	136	364	265	286	27	78
25	59	111	278	216	233	15	45
26	60	208	598	406	438	35	160
27	60	165	514	322	347	48	192
28	60	197	420	304	328	28	92
29	61	148	540	288	311	73	229
30	61	163	530	318	343	54	187
31	65	136	325	266	287	13	38
32	66	195	578	378	408	41	170
33	67	136	412	265	286	44	126
34	67	146	295	285	307		
35	67	119	450	232	250	80	218
36	69	147	295	287	309		
37	70	145	450	283	305	47	145
38	72	115	265	224	242	9	23
39	72	118	373	228	246	51	127
40	72	140	614	273	294	108	320
41	74	134	470	261	281	67	189
42	75	180	420	351	378	10	41

* All patients were men.

were examined at the clinic their readings of blood pressure were normal. We believe it is not unreasonable to assume that if these patients previously had had hypertension that was severe enough to produce cardiac hypertrophy, either they themselves would have been aware of it, or some evidence of it would have been revealed by examination. We excluded all cases of chronic valvular disease, all cases of syphilitic aortitis with aortic insufficiency, all cases of congenital heart disease, and all cases of hyperthyroidism, nephritis and pericarditis (except the pericarditis that occurred with the infarction). We also excluded cases of emphysema and of marked fibrosis of the lungs, and all cases of severe anemia.

All the patients were men. Their ages at the time of death varied from 35 to 75 years. Two were between 35 and 39 years of age; 4, between 40 and 44 years; 19, between 50 and 59 years; 11, between 60 and 69 years, and 6 between 70 and 79 years. Roentgenologic studies of the hearts were made in 30 cases: Thirteen were reported to be moderately to markedly enlarged; there were 17 cases in which the roentgenologic report revealed no enlargement. There were 25 cases in which the heart was the primary cause of death, and in 17 cases it was not.

It has been proved and accepted by investigators that there is definite ratio between the normal weight of the body and the normal weight of the heart. Large persons normally have large hearts and small persons small hearts. For example, a heart weighing 400 gm. taken from a man who weighed 200 pounds may be well within the limits of normal for that man, but a heart of this weight, taken from a woman who weighed 105 pounds, would be almost double the normal weight for her. The ratio is 0.43 for adult men and 0.40 for adult women. The ratio is slightly higher than normal among thin persons and lower than normal among obese persons. The normal weight of the heart of the adult may be deduced from the body weight with an error of about 8 per cent. The coefficient is not so accurate among persons whose bodies are extremely obese or extremely light. We believe it is not possible to make an accurate study of cardiac weights without considering body weights.

In this series of 42 cases, the weights of the heart were in excess of normal in 37 cases (88 per cent). There were 5 patients whose cardiac weights were well within the limits of normal. The largest heart weighed 715 gm.; the smallest, 265 gm. The greatest relative increase was in a case in which the heart weighed 614 gm.; an increase of 341 gm., or 108 per cent, and that is allowing for an error of 8 per cent, as has been shown previously. There was another heart that weighed 715 gm.; in this case, the absolute increase in weight was 358 gm., but the percentage increase was 85 per cent after allowance was made for a probable error of 8 per cent.

Our data are summarized in the table. In 5 cases, the cardiac weight was normal. Otherwise, the minimal increase above normal

is 9 per cent and the maximal increase, 108 per cent. The average increase for the whole group is 44 per cent.

Summary and Conclusions. A study has been made of the weights of the heart in 42 cases of cardiac infarction, in which all other known or supposed causes of cardiac hypertrophy have been excluded. Of the 42 cases, in 37 (88 per cent) there was definite gross cardiac hypertrophy. In 5 cases the weights of the hearts were not above normal. The minimal increase in weight was 18 gm. (9 per cent); the maximal increase, 341 gm. (108 per cent), and the average increase, 132 gm. (44 per cent). From the data given it would appear that cardiac infarction is a definite cause of cardiac hypertrophy.

BIBLIOGRAPHY.

1. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body, and of the Weight of the Heart to Age, *Am. Heart J.*, 1928, 4, 79.

SPONTANEOUS RUPTURE OF THE AORTA.

BY OSKAR KLOTZ,

AND

WINIFRED SIMPSON,

TORONTO, CANADA.

(From the Department of Pathology and Bacteriology, University of Toronto.)

THIS title might suggest that under certain circumstances the normal aorta ruptures through inability to withstand the ordinary pressure within it. There has been much controversy about this point, some stoutly maintaining that the undamaged aortic wall may at times be placed under such stress as to give way in sudden and fatal hemorrhage, while others are equally convinced that no spontaneous rupture is possible without antecedent damage or degeneration of the vascular tissues. It is obvious that in discussing the condition of spontaneous rupture, we must confine our attention to those instances in which no antecedent clinical or pathologic evidence of a progressive lesion was noted, and in which also no unusual extraneous factors have imposed themselves, which could be held directly accountable for the severe tissue lesion and fatal hemorrhage. Thus, we omit those cases that follow falls from considerable heights (buildings, aeroplanes and bridges). Under those circumstances the aorta, normal or diseased, bursts because of the sudden increase of blood pressure within it resulting from the impact of the blood and from the doubling up and distortion of the body as it strikes the ground. It is the explosive force of the contained blood which rips through the aortic wall. Nor will we consider the

progressive destruction of a syphilitic aortitis which leads to aneurysm and so commonly to sudden fatal hemorrhage or to slow leakages into neighboring hollow viscera and body cavities. Occasionally what appear to be cases of spontaneous rupture of the aorta are shown to have had their hemorrhage from unrecognized and obscure aneurysms. Some authors have preferred the term "idiopathic" in place of "spontaneous" rupture of the aorta, preferring the meaning "without apparent extrinsic cause" to that of "unassociated."

The majority if not all cases of spontaneous rupture of the aorta are associated with some degree of dissecting aneurysm. This need not always be the case, but as we shall indicate later, the conditions which predispose the aortic wall to dissecting aneurysm are the same as those which permit the vessel to suddenly give way in rupture. In truth, every dissecting aneurysm is an incomplete rupture of the aorta.

If, then, we are able to determine the underlying factors which predispose a vessel for the development of a dissecting aneurysm, we shall be able to understand the causes which play a part in a large proportion of spontaneous ruptures. Not all cases belong to this class, as there are other conditions which independently predispose the aorta to rupture. These may be classified as: (1) Trauma; (2) acute mycosis of aorta; (3) exogenous erosion of aorta (tuberculosis or abscess); (4) syphilis of aorta, and (5) vermicular infestation of the aorta (as seen in spirocerca infection of dogs). Here the reason for the rupture of the aorta is obvious and cannot be classed as spontaneous or idiopathic. But in the remaining group, where no clinical or pathologic factor is demonstrable to the naked eye, and where the patient has shown no progressive ill health, the explanation for the occurrence of sudden fatal hemorrhage is frequently difficult to indicate.

It is apparent that, if a dissecting aneurysm is an incomplete rupture of the aorta, a certain proportion of the cases of complete rupture will have begun as the usual dissecting aneurysm, but continued to the production of a perforating tear. This is true in the greater number of cases, and particularly of those above the age of 40. Dissecting aneurysms are usually found after 40, the relative incidence increasing with advancing years. A dissecting aneurysm begins as a tear through the inner layers of the aortic wall, then by separating the layers of the outer part of the media it excavates a cavity in a longitudinal and circular manner. The dissecting aneurysm may perforate outwardly through the remaining portions of the aorta, or it may perforate inwardly to communicate again in its distal portion with the aortic lumen. When external perforation has not completely ruptured the vessel, the dissecting aneurysm does not lead to immediate death, and its cavity may be reclothed by an endothelial membrane. The literature contains upward of 350 cases of dissecting aneurysm. One feature in true

dissecting aneurysm is constant: the dissection of the aortic wall giving rise to the aneurysm has taken place between the lamellæ of the media, usually in its middle or outer third. Blood masses lying in the loose stroma along the course of the aorta, even though communicating with the aortic lumen, are not true dissecting aneurysms. Furthermore, syphilis of the aortic wall is not a factor in the production of true dissecting aneurysms, as the very nature of the syphilitic process with its gumma and fibrosis does not render the vessel liable to dissection. In fact, the granulomatous inflammatory invasion of the arterial wall will tend to weld the neighboring laminae more closely together so that the wall may be less readily split into its anatomic layers than normally.

Considering the structure of the wall of the aorta, the normal intima is a delicate layer superimposed upon the internal elastic lamina with its stratum of longitudinal muscle fibers. The media is the important structure, composed of alternating elastic bands and circular muscle fibers. It is relatively thick and endowed with great strength. In its outer third it is supplied by an abundance of small bloodvessels, the vasa vasorum, which are distributed to it from the adventitia. These nutrient vessels have their origin from different small branches arising from the aorta, such as the coronaries of the heart, the intercostals, the vessels of the neck and the various abdominal arteries. Woodruff has recently demonstrated small nutrient vessels arising directly from the aorta itself; Robertson, in our laboratory, has found similar vessels. The inner two-thirds of the media of the human aorta contains no bloodvessels. It has been noted that, with disturbances of the vasa vasorum, marked changes may occur in the portion of the aorta nourished by them. The outermost portion of the media is bounded by an irregular mass of elastic fibers, spoken of as the external elastic lamina. Beyond this layer lies the adventitia made up of a matting of connective tissue, elastic fibers, some muscle cells and small bloodvessels.

As the strength of every artery lies in the strength of its medial coat, it is obvious that whenever aneurysm develops upon a vessel, the middle coat has been damaged. The pouching, stretching or ripping of the arterial coat is induced by the blood pressure acting upon an area of weakness. What is true, in general principle, for aneurysm is also true for rupture of the aorta. However, the question frequently arises: how far is the heightened blood pressure alone responsible for the rupture of an apparently normal artery? We have examined the aortas of individuals between the ages of 20 and 40 and subjected them to pressures of 1000 mm. of mercury without producing rupture. Oppenheim states that rupture of the aorta will not occur until a pressure in the neighborhood of 3000 mm. of mercury is reached, a pressure about 20 times that of normal. As these analyses were all determined at postmortem when the vessels were in a state of cadaveric rigidity it is possible that the

figures will differ from those necessary to burst a living vessel. This point was investigated in the aortas of rabbits by Schnurbein who found no difference in the resistance to pressure between the aortas of freshly killed animals and those showing postmortem rigidity. Hence, one is forced to realize that in the uninjured aorta a tremendous internal pressure is necessary to produce rupture of its wall, a pressure much greater than can be developed by the cardiovascular mechanism alone.

It would seem obvious that damage to the wall of the aorta preceded the occurrence of rupture; but a number of cases, about 40 in all, have been reported in individuals under 40 in whom no adequate explanation is available. Let us dismiss from consideration all cases over 40 years, for in them there is always some degenerative change in the muscle and elastic elements of the media. A vessel so afflicted no longer possesses its juvenile pliability, and the arterial coat is actually more friable, readily splitting into two lamellæ through the media. The aorta of a child or youth maintains its normal elasticity for some hours after death, and such an aorta has its several layers of tissue firmly bound together so that they cannot be separated. The aortas of old age possess an unusual dryness and friability which, in a measure at least, account for the tendency to develop dissecting aneurysms and spontaneous ruptures.

Below the age of 40 or thereabouts, the presence of well-marked degenerative changes in the media, sufficient to show a weakness in the union of the neighboring laminae, is unusual. It is in these in which occasionally a sudden rupture of the aorta takes place and an examination of the wall may fail to reveal an adequate lesion.

A number of authors have observed an hypertrophy of the heart in association with rupture of the aorta (Busse, Schlipp). The presence of the hypertrophied heart is taken as evidence of an increased blood pressure. Furthermore, others have noted the occurrence of chronic nephritis in a certain number of these cases. However, the cases in which the evidences of chronic cardiorenal disease were noted were individuals beyond middle life, in whom a certain amount of heart and kidney disease is not unusual. In a few others a more direct relation could be associated with the presence of a narrowing of the aorta just above the level of the ductus arteriosus. This condition of coarctation of the aorta is accompanied by a dilatation of the ascending limb and arch of the aorta along with an hypertrophied heart. Enlargement of the anastomosing systemic vessels is usually present and there is adequate evidence, that the portion of the aorta which is in direct continuity with the heart suffers a definite increase in blood pressure. Degenerative changes may then involve these aortic structures, weakening the wall and occasionally leading to rupture.

Babes and Mironescu observed the occurrence of rupture and dissecting aneurysm of the aorta in a woman aged 51. They believed

that the primary condition was one of hypertension which had gradually led to the production of multiple fissures in the tissues of the media, and by coalescence had so weakened the vessel wall as to allow the occurrence of spontaneous rupture associated with a dissection of the middle coat. The authors were convinced that definite spaces were present in the wall, induced through the influence of high blood pressure. It is difficult to understand how such lesions could develop under the influence of hypertension. Other factors than an increase in blood pressure must be at work before lesions with necroses of muscle cells and elastic fibers can give rise to these faults in the middle coat.

Spontaneous rupture of the aorta has been described in early youth, Rokitsansky encountering the lesion in a boy of 8 years, Oppenheimer in a girl of 9 years, Wasastjerna in a boy of 13 years, while quite a number of cases have been reported in individuals of 20 to 30 years of age. Although some of the authors claim to have searched diligently for evidences of lesions in the aortic wall near the site of rupture, and state that they were unable to demonstrate them, one cannot be entirely satisfied that the various methods used for demonstrating changes in elastic fibers, muscle fibers and lesions in the vasa vasorum, have been sufficiently well applied to accept unreservedly the statement that the arterial wall was normal. It is obvious, of course, that if the tear or the dissecting aneurysm, passes through the areas of injury in the aortic wall, little will be left within that tissue to indicate the condition of the structures at the point of the tear. The evidence that the neighboring muscle and elastic fibers show but little change in their character is not sufficient proof that an area of weakness and damage did not lie in the path of the rupture. In a few cases, Babes and Mironescu, Krukenberg, and Bay observed the presence of focal degenerations and necroses in relation to the vasa vasorum in the media. These authors found areas of degeneration, cysts, or hemorrhage in portions of the arterial wall not involved in the rupture or dissecting aneurysm. They believed that these lesions represent the points of weakness and that the splitting of the artery occurred along their path. In some of the cases the vasa vasorum showed obliterating endarteritis, thrombosis, necrosis and hemorrhage, so that a cleft was produced which led to a separation of the layers of the artery and only subsequently did a perforation occur between the lumen of the vessel and the cavity within its wall.

Recently Gsell, studying a number of cases of rupture of the aorta, found that the vessel wall had suffered noninflammatory necrosis of the media. He compares the lesions to those previously described by Wiesel, who had noted the presence of peculiar focal necroses in the vessel wall of young individuals dying of acute infections. It is suggested that these necroses are the result of toxic damage of the muscle elements along with changes in the elastic tissues. They have no direct relation to lesions arising in the intima.

Erdheim in a careful study of a case of spontaneous rupture observes lesions similar to those described by Gsell and notes that patches of necrosis and peculiar hyalin vacuolization of the media were present in the aortic wall beyond the region of rupture. The muscular elements as well as the elastic fibers and connective tissues were involved. The absence of an inflammatory reaction was striking and there was little attempt at repair. The necroses were particularly evident in the outer two-thirds of the media. The destructive process in the media leads to disintegration of the cellular elements and the dissolved materials are absorbed without local tissue reaction. These areas may subsequently become infiltrated by an albuminous fluid leading to peculiar cystic spaces between neighboring elastic fibers. These findings were supported in a further investigation by the same author, who studied more carefully the mucoid degeneration of the wall and the development of necrotic cysts. He carefully differentiates the process of necrosis of the media from the process of mucoid degeneration, but is unable to clearly determine the factors of causation although he points out the possibility of toxins playing an important rôle.

In 5 cases of spontaneous rupture, which came to our attention, somewhat similar lesions were encountered, which we believe played a part in the subsequent rupture and fatal hemorrhage of the aorta. In each case a dissecting aneurysm had occurred along with the rip of the aorta.

Case Histories. CASE 1.—S. W., a female, aged 23 years, was pregnant about 8 months and felt well until midnight of October 19, 1925, when she suddenly developed a terrible attack of anginal pain confined to the precordium and radiating to the left back. This attack was associated with marked dyspnea and the sensation of choking. The pain, which was partially relieved by morphin, lasted 2 or 3 hours and recurred on the following two nights when she had some vomiting.

She had scarlet fever at the age of 6, and influenza in 1918. No history of rheumatic heart disease or of syphilis.

The patient was admitted to the Hospital on October 22d, stating that she was free from pain. The pulse rate 110 with extrasystoles every third or fourth beat; slight systolic and diastolic murmurs in the aortic area. No cyanosis, no edema of extremities; liver not enlarged and lungs clear. Temperature was normal, respirations 20 to 28. Wassermann reaction negative. Blood pressure 110/50. Patient was kept in bed. Five days after admission she had dyspnea, cyanosis, but no pain. She died suddenly while resting quietly in bed on October 31st, 12 days after the onset of the attack.

Autopsy. The body was that of a young, adult, white female, with the signs of pregnancy, enlarged breasts and enlarged uterus containing a fetus of about full-term proportions.

The lungs were found normal except for a few old pleural adhesions.

The pericardial sac was markedly distended and tense and filled with 600 cc. of fluid blood.

Heart and Aorta. The heart was about usual in size, and was surrounded by the fresh clotted blood within the pericardial sac. There were no adhesions or signs of recent inflammation in the pericardium. The epicardium

contained a fair amount of yellow fat. At the root of the aorta just above its junction with the base of the heart, there was a slitlike perforation 0.8 cm. in length which entered the aorta and freely communicated with the pericardium. It lay along the left anterior aspect of the root of the aorta in close proximity to the pulmonary artery. The edges of the rupture were sharp, as if made by a knife; the external surface of the opening showed a slight blood infiltration of the surrounding tissue and had the character of a recent tear. Upon opening the heart the cavity on the right side was normal; the tricuspid measured 9 cm., the pulmonary 5 cm. They were thin and elastic and were without change. The left ventricle showed some hypertrophy, being 2 cm. in greatest thickness. The mitral valve measured 8.5 cm. and showed a slight amount of transparent thickening close to the free margin.

In approaching the aortic orifice from the left ventricle a peculiar appearance presented itself prior to cutting the ring. It was found that the aortic leaflets were invaginated into the conus of the ventricle, suggesting prolapse not only of the leaflets themselves, but also of the tissue of the aortic ring upon which valvular structures were attached. The entire aortic orifice appeared to be blocked by a mass of tissue projecting from the aorta.

Aorta. An annular transverse tear was found in the base of the aorta at a distance of 0.5 cm. above the aortic leaflets. The tear was sharp and its edges appeared as if made by a knife; it passed completely about the circumference of the aorta save for a small bridge 0.5 cm. in width which maintained the continuity between the proximal and distal portions of the aorta. The rupture of the aortic tissue occurred only in transverse direction and did not produce stellate tears. The tear through the aortic wall was not complete, but entered the deep portion of the media and then led to a peeling off of the proximal portion of the aortic wall so as to produce a local dissecting aneurysm. The dissection of the aortic coat extended from the transverse tear toward the aortic ring, excavating the inner two-thirds of the aortic wall behind the sinuses of Valsalva and down to the lower edge of the aortic cusps. The dissecting aneurysm was 3.5 cm. in its greatest length. Thus a collar of a dissecting aneurysm occupied the base of the aorta. The aneurysm did not progress beyond the coronary arteries, both of which were given off from the aorta above the level of the left posterior aortic valve cusp. In the cavity of this recent dissecting aneurysm there was some fresh, slightly adherent clot. The walls of the aneurysmal pouch were clean and pink in appearance. In some places a thin film of fibrin could be seen covering the surface. The walls of the aneurysm, in the vicinity of the perforation, showed a great quantity of this grayish deposit. The perforation which extended from the lumen of the aorta to the pericardium was found to lie within the area of the aneurysm and to possess a slitlike orifice around which there was no evidence of thrombus or an inflammatory exudate. There was no evidence of dissection of the aortic tissue in the upper direction, but it was found that immediately above the point of perforation the tear had entered the loose tissue lying between the aorta and pulmonary artery. There were some superficial fatty streaks in the descending thoracic aorta. The aorta was elastic and of usual consistency for a young individual showing no evidence of syphilis, arteriosclerosis or atheroma. There was nothing to indicate, in the naked-eye examination, an antecedent disease process with which the tear of the aorta and separation of the aortic coats could be associated.

Anatomic Diagnosis. Rupture of ascending aorta; laceration of aorta; hemopericardium; dissecting aneurysm of aorta (slight); old bilateral pleural adhesions; pregnancy; (sudden death).

Résumé. This was a case of sudden death in a pregnant woman of 23 years, in whom an extensive rupture of the aorta had taken place without

the presence of macroscopic change in the aortic wall. She suffered a severe anginal attack 12 days before death and continued in distress, save as relieved by morphia. She had no acute infection and the Wassermann reaction was negative. Blood pressure 110/50. She died suddenly while resting in bed. The autopsy revealed a transverse tear of the aorta 0.5 cm. above the aortic cusps. Below the level of the aortic tear a dissecting aneurysm was produced reaching to the insertion of the aorta upon the heart. A small perforation extended from the dissecting aneurysm into the pericardium leading to the filling of the pericardial sac with blood.

CASE 2.—R. M., male, aged 45 years, a salesman, was admitted to hospital May 23, 1927; for six weeks he had suffered headaches and attacks of vomiting; also had frequency and hematuria. One week later he complained of dimness of vision which became steadily worse. In 6 weeks lost 10 pounds.

Patient is stuporous, speech slow, no respiratory distress. Respiratory system showed nothing of note. Cardiovascular system, apex beat 10 cm. from midline in 5th interspace; blowing systolic mitral murmur; pulse regular; radial, brachial and femoral arteries palpable and thickened; blood pressure 210/140. Liver slightly enlarged. Urine, 24-hour specimen 960 cc.; acid, specific gravity 1016, albumin present, blood present, granular casts. Wassermann reaction negative. Patient died suddenly 4 days after admission.

Autopsy. The body was that of a well-developed and well-nourished middle-aged man. The external surfaces of the body showed a number of ecchymoses of the skin, but otherwise nothing of note.

The heart and pericardium occupied an area measuring 14 cm. in length by 16 cm. in width. Both pleural cavities were free from adhesions and excess fluid. The pericardium was smooth and glistening. The heart lay free in its cavity which contained a large amount of dark red recent clot which entirely surrounded the heart. It was distinctly enlarged, particularly on the left side but also to some extent on the right. It measured 12.5 by 15 by 7.5 cm. There was a fair amount of epicardial fat. The epicardium showed no evidence of recent or old inflammatory change. The left ventricle measured 2.75 cm. in thickness and was fairly well contracted. The musculature was firm and dark red and there were no areas of fibrosis. The valve orifices measured, tricuspid, 12 cm.; pulmonary, 7 cm.; aortic, 7.5 cm.; mitral, 10.5 cm. The leaflets were thin and elastic with no evidence of old or recent inflammation. The coronary arteries were patent throughout, showing occasional yellow atheromatous plaques along the course of the main branches.

Aorta. The ascending aorta measured 7 cm. in circumference. The wall appeared to be of usual thickness and the inner surface was quite smooth, save for a few stippled areas of fatty change. In the transverse arch and continuing into the descending arch, there was considerable nodular endarteritis and atheroma, particularly in the vicinity of the outlet of the vessels of the neck. The important lesion in the aorta lay in the ascending aorta 3.5 cm. above the aortic cusps. This portion of the aorta showed the least amount of intimal change. The lesion consisted of a transverse tear of the aortic wall 2 cm. in length. This tear was sharp and knifelike, passing through the entire thickness of the aorta but at the right border leading into a pocket of a dissecting aneurysm. The borders of the tear showed no evidence of ulceration, inflammation or deposition of fibrin. In the vicinity of the tear and for about 2 cm. toward the aortic cusps the wall was seen to be more translucent than elsewhere. The tear had progressed through the media and adventitia, entering the loose tissues between the aorta and the pericardial sac. Blood had escaped through the rupture, causing a hematoma protrusion beneath the pericardium and outside of the aorta, meas-

uring about 5 by 6.5 cm. At one point was found an opening through the pericardial covering, through which the blood had escaped into the pericardial sac. In dissecting the aorta on its outer surface, it was found that the sac which had formed outside the area of rupture had actually dissected some of the tissues of the aortic wall, and that the covering was not merely composed of loose pericardial structure, but included the outer layers of the aortic wall. On exploring this outer sac, it was found to extend from 1 cm. below the origin of the innominate artery, encircling the right border of the ascending aorta downward to the point of insertion of the aortic valves. The inner surface of the cavity showed the striations of the circular muscle bundles of the aortic wall. Upon these surfaces, a thin film of fibrin had been deposited along with small blotches of red blood. There was, however, within the cavity no evidence of a thrombus. On viewing the rupture from the posterior surface, it was found that the tear was not as clear cut as would appear from the intimal side, but had passed through succeeding layers of muscle tissue, raising successive lamellæ of these structures during the passage. The manner in which the layers of the media had been separated from each other, bringing about a division of the media in its outer third, was quite similar to the appearance which we encounter when the aorta of an elderly person is divided into two parts by splitting the media and stripping these coats apart. The appearance which we found in this specimen suggested the presence of a potential, but not actual, cavity in the outer portion of the media and that the rupture through the inner wall (consisting of the intima and inner two-thirds of the media) was only a final event in an inherently weakened wall. On carefully exploring the sac in a downward direction, it was found that it passed to the aortic ring and encircled the right coronary artery. It was noted that the dry and brittle character of the aorta extended beyond the sac of the dissecting aneurysm, for it was possible to continue the separation of the wall of the aorta by moderate tension upon the walls of the sac.

Anatomic Diagnosis. Rupture of aorta; hemopericardium; chronic nodular endarteritis of aorta and atheroma of coronary vessels; hypertrophy and dilatation of heart; chronic interstitial nephritis; dissecting aneurysm of aorta.

Résumé. A man, aged 45 years, suffering from chronic Bright's disease and having a high blood pressure, died suddenly without symptoms referable to the heart. Wassermann reaction negative. At autopsy there was disclosed a transverse knifelike rupture of the aorta 3.5 cm. above the aortic valve. The rupture led to the development of a local dissecting aneurysm, the perforation of which into the pericardial sac had caused death. The aorta at the site of rupture was thinner than normal, due to bandlike necroses occupying the media.

CASE 3.—Mrs. M. B., aged 54 years, has suffered from headaches for 4 years. Recently these have been increasing and accompanied by vomiting. She has had a history of rheumatism and recurrent attacks of precordial pain. On April 14, 1931, she was suddenly seized with a severe pain in the neck, rapidly spreading to the shoulders and to the chest. The pain became so severe that she required morphin and she vomited. Temperature 99.4°, pulse 86, and respirations 22. Lungs, negative. Heart, slightly enlarged; occasional extrasystole. Blood pressure, 190. Palpable vessels somewhat sclerosed. Abdomen, negative. Wassermann test negative. Blood: white blood cells, 20,500; polymorphonuclears, 90 per cent.

The dull pain across chest persisted from day to day. There was dullness at the base of the left lung; a friction rub was heard at the apex of the heart. Aspiration of the left chest yielded 250 cc. of blood-stained fluid. On April 30th, while taking a bath, the patient suddenly collapsed and died, 16 days after onset.

Autopsy. The body was that of a well-developed middle-aged woman, in whom the main findings at necropsy were related to the cardiovascular system. Within the chest the outstanding feature was an enormously ballooned pericardium measuring 18.3 cm. in width, and filled with a large mass of fluid and recently clotted blood.

Heart and Aorta. The heart and aorta were kept attached as one specimen. Some of the clotted pericardial blood had developed tough fibrinous attachments to both the parietal and visceral pericardium. It was possible to distinguish blood which had been evacuated just prior to death, and some

phase of organization. The pericardial sac showed no evidence of a primary inflammatory process. The heart lay enveloped in the mass of blood, so that none of its surface could be seen. On exploring the pericardial sac at the base, it was found that there was a laceration at a point immediately above the level of the left ventricle, where this structure was inserted onto the base of the aorta.

The heart was firmly contracted. The wall of the left ventricle was quite thick (2.5 cm.) and firm. The cavity of the left ventricle was small, not dilated, and showed some white patches of pearly endocardial thickening. The aortic orifice measured 5.5 cm. and the aortic valves were normal. The mitral orifice was not narrowed, but the edge of the cusps were slightly thickened and on the posterior surface were some fatty plaques. The pulmonary orifice measured 5 cm. and was normal. The tricuspid orifice measured 9.5 cm. and showed no change. The heart muscle showed numerous patches of fibrosis, particularly along the endocardial border. The coronary artery showed some sclerosis but no marked narrowing of the lumen was observed.

Aorta. On opening the aorta it was found that its wall had been split into a double layer from the aortic ring to its bifurcation in the abdomen. Into this space there had been an escape of blood which encircled the aorta in all its parts. This formed a layer of varying thickness, the greatest being found at the arch, where it measured 1.5 cm. and was interposed over its convex portion. This dissecting aneurysm encircled the vessels of the neck and surrounded the mouth of the innominate artery; otherwise it did not extend along any of the branches coming from the aorta. It had its beginning in a transverse tear within the intima of the arch of the aorta immediately opposite to the origin of the innominate artery, 9 cm. above the aortic valves. The tear across the aorta was 5.5 cm. in length and involved the aorta in more than three-quarters of its circumference. At the point of tear there was no evidence of atheroma or ulceration. The rupture was a single linear division with sharp knifelike edges. The tear led through the intima into the media where the separation took place leading to the dissecting aneurysm. The inner wall of the dissecting aneurysm formed a layer about the thickness of ordinary blotting paper, while the outer wall, composed of the outer part of the media, adventitia and periadventitial connective tissues, was thicker than the inner boundary.

The aneurysm caused a considerable bulging in the ascending limb of the aorta and gave rise to a protrusion of the aorta within the pericardial sac. Over this bulging mass the outer coat of the dissecting aneurysm had given way and led to hemorrhage into the pericardium. Furthermore, the mass of blood occupying the dissecting aneurysm at the root of the aorta led to an irregular bulging of the intima narrowing the lumen of the aorta.

The intimal surface of the aorta was clear and without evidence of change in its first portion up to the point of rupture in the arch. From this point onward, there was a nodular endarteritis, particularly about the exit of the intervertebral arteries. These nodular thickenings were smooth and pearly white, many with some atheroma about them. Between these pearly

nodules the wall of the aorta was wrinkled and in places showed a peculiar atrophic depression of the surface. These intervening portions were more transparent than normal and suggested an actual loss of tissue in their bases. The longitudinal wrinkling at first sight suggested a syphilitic process, but on closer examination it was noted that no stellate scars were present.

The blood lying in the dissecting aneurysm was found laminated and well clotted. In some regions the clot was very adherent to the walls and appeared older. Furthermore, it was noted that the outer wall of the dissecting aneurysm with its periadventitial tissues was edematous and thick.

Anatomic Diagnosis. Rupture of aorta; dissecting aneurysm of aorta; hemopericardium; hypertrophy and dilatation of heart; chronic nodular endarteritis of aorta and coronary arteries.

Résumé. A woman, aged 54 years, with a history of rheumatism and recurrent precordial pain, was suddenly seized with an anginal attack which was relieved by morphin. Although fairly comfortable for a period of 16 days she died suddenly with a hemopericardium. The Wassermann reaction was negative. There was a transverse tear of the ascending aorta which led into a dissecting aneurysm involving the aorta from the heart to the iliac arteries. The blood within the aneurysm was undergoing organization, indicating that the aneurysm had been produced some days, probably 16, before death. The final rupture into the pericardium took place at the time of death. The inner aspect of the aorta had a peculiar corrugated appearance, suggesting at first sight a syphilitic process. These areas, however, were depressed and were located over necroses of the media.

CASE 4.—Mrs. G. S., aged 39 years, for the past 2 years had suffered from recurrent attacks of dyspnea and palpitation. She had been subject to headaches which had been more frequent during the last 2 weeks. She was pregnant at about the sixth month. On May 13, 1931, she developed a sudden severe pain between the shoulder blades and on the right side of the chest. The right arm and hand became blanched and the veins of the neck and upper chest became engorged. The patient rapidly collapsed as in a state of shock. About an hour after the onset she vomited some fluid containing blood, and 4 hours later she passed blood by rectum. Temperature, 98°; respirations, 38; pulse, 114. Blood pressure 100/30. The heart was found enlarged; a soft presystolic murmur was heard at the apex and a harsh systolic murmur in the second right interspace propagated into the neck. Blood: white blood cells, 12,200; polymorphonuclears, 93 per cent. The patient was stuporous; no evidence of paralysis; lungs show some moist râles. She vomited large quantities of blood-stained frothy fluid and died suddenly 13 hours after onset of acute symptoms.

Autopsy. The body was that of a middle-aged woman, about 6 months pregnant, in whom the outstanding pathologic findings were related to the heart and aorta.

Each *pleural cavity* contained about 500 cc. of a clear fluid, while the lungs showed some evidence of edema.

The *heart* was distinctly hypertrophied, particularly in its left ventricle. The valve orifices were not narrowed, although both the mitral and aortic cusps showed some thickening along the free borders. Scattered areas of fibrosis were present in the wall of the left ventricle and in the papillary muscles. In the right auricle opposite the insertion of the aorta into the heart was a blotch of hemorrhage corresponding to the base of the dissecting aneurysm, which will be described below. The endocardial surface of the left auricle showed some rheumatic scarring. The coronary arteries showed considerable sclerosis and narrowing, especially the left descending branch and the main trunk of the right coronary.

Aorta. The ascending limb immediately above the aortic ring measured 9.5 cm. in circumference. The inner surface was smooth, showing only

slight superficial deposits of fat. At a point 1 cm. above the level of the insertion of the aortic cusps was a transverse tear almost completely encircling the aorta except for a narrow isthmus 1.5 cm. in width. This tear was of recent origin, its edges were sharp and it passed through the inner two-thirds of the thickness of the aorta into a recently developed sac, which was filled with fluid blood and a few stringy coagula. A dissecting aneurysm was thus formed, completely enveloping the aorta, bounded on the outer side by part of the media and the adventitia. The dissection had occurred toward the heart, passing behind the sinuses of Valsalva down to the insertion of the aorta into the myocardium. It had also encircled the margin of the anterior coronary artery. There was no old clot within any portion of the dissecting aneurysm. The aneurysm had not burst into the pericardial sac.

The dissection had progressed distally from the heart along the entire course of the aorta, in some places completely encircling the vessel, while in others it extended only partially around its circumference. Opposite the bifurcation of the trachea there had been some escape of blood into the neighboring soft tissues. Within the cavity of the dissecting aneurysm, which throughout was composed of the divided wall of the aorta, there was some fluid blood and some recent coagulum. In those portions where the splitting of the laminae had not led to pouching it was noted that the tissues could be separated with remarkable ease in the manner in which the dissecting aneurysm was produced. The dissection was followed down to the bifurcation and extended for a short distance into the wall of the iliac arteries.

On viewing the aorta from its inner surface, very little change of the intima was noted in its thoracic portion. A few small diffuse areas of endarteritis and some splashes of superficial atheroma were noted, also some peculiar groups of longitudinal grooves, somewhat suggesting syphilis but lacking the stellate character. Some escape of blood was noted into the soft tissues about the crus of the diaphragm.

The abdominal aorta showed marked sclerosis of its wall below the level of the renal arteries. This sclerosis consisted of flat calcareous plaques which seemed to lie directly beneath the intima and over which no intimal thickening had occurred. These had the appearance of the small crater-like calcareous plaques seen in the aorta of experimental arteriosclerosis, such as induced by adrenalin, nicotine and other drugs.

Anatomic Diagnosis. Rupture of aorta; dissecting aneurysm of aorta; chronic nodular endarteritis of aorta; arteriosclerosis of coronary arteries.

Résumé. A pregnant woman, aged 39 years, had a history of recurrent attacks of dyspnea and palpitation for 2 years. She developed a sudden attack of angina and died within 13 hours of the onset. The autopsy disclosed a rupture of the ascending aorta leading into a dissecting aneurysm, extending from the aortic valves to the pelvis. The point of rupture showed no inflammatory process nor atheroma of the intima, but there was extensive mucoid degeneration of the media at this point. The dissecting aneurysm followed a course between the middle and outer third of the media. Throughout the aorta there were patches of degeneration of the muscle elements of the outer part of the media. The lesions were similar to those described in previous cases. It was also interesting that a similar type of degeneration was present in the musculature of the renal, splenic and coronary arteries. Inasmuch as the aneurysm was of recent date, no clotted blood was found between the torn areas of the aorta.

CASE 5.—E. C., aged 38 years, was admitted to hospital on May 30, 1931, in a semistuporous condition. He had been in good health until December, 1930, when he developed lumbosacral pain. He also complained of dizziness and double vision. For the previous 2 weeks he had had marked

dyspnea and palpitation on exertion. Occasional attacks of nausea were relieved by vomiting.

Twenty-four hours before admission the patient developed acute abdominal pain with nausea and vomiting. Temperature, 100.6°; pulse, 106; respiration, 20; blood pressure, 220/150. Urine, albumin +++; casts, red blood cells and white blood cells; blood hemoglobin, 110; white blood cells, 19,000; Wassermann reaction, negative.

For the first few days in hospital patient appeared to be improving, but low-grade fever continued. On June 9th he became restless, with some evidence of spasticity of right arm and leg. Later he developed a motor aphasia. June 13th patient suddenly collapsed, and died 5 hours later.

Autopsy. The body was that of a well developed male, showing well-marked cerebral arteriosclerosis with softening of brain in the left hemisphere. There was also a recurrent interstitial and glomerulonephritis. The left pleural cavity was filled with blood.

Heart. The heart was of good size, the epicardium was covered by a fair amount of fat. There was no evidence of blood in the pericardial sac. The valvular orifices appeared normal and there was no evidence of old or recent endocarditis. The myocardium of the left ventricle was very thick, measuring 2.5 cm. The musculature was firm and well contracted. There was also some increase in the thickness of the right ventricle, measuring 0.8 cm. in its mid portion. The sclerosis was diffuse and affected both the right and left coronaries. There was some fibrosis in the left ventricle.

Aorta. The aorta had a remarkable and distorted appearance showing abnormal bulgings at the root of the aorta within the pericardium, as well as over the descending arch on the left side. The bulging mass in the pericardium was of a purplish-red color and consisted of a sac of blood covered by the thin pericardial membrane and appeared ready to burst. This mass was the size of a hen's egg, measuring 5 by 3.5 cm. in diameter.

The mass over the descending arch was still greater in size, measuring 8 by 5 by 5 cm. The surface was covered by the pleura and was hemorrhagic, there being some adherent blood clot protruding into the left pleural cavity. Other bulgings were also noted in the lower portion of the abdominal aorta just above the bifurcation and along the course of both iliac arteries. On opening the aorta the intimal surface of the ascending limb, and the arch were quite smooth and yellowish-white in color, while in the lower portion of the thoracic and abdominal aorta there were some nodular thickenings of the intima.

In the thoracic aorta opposite the level of the first pair of intercostal arteries, there was a knifelike transverse tear on the anterior portion partially encircling the vessel. This tear extended through the inner wall into the cavity between the two lamellæ in an upward and downward direction. This separation or dissection of the aortic wall extended throughout the length of the vessel from the sinus of Valsalva to and including both iliac arteries; the dissecting process also involved the left carotid and left subclavian arteries. The two bulging masses referred to above consisted of large hematmata arising from this dissecting process and leading to the infiltration of the periaortic tissues in both these regions. The hematoma at the root of the aorta measured 2.5 cm. while that over the arch was 4.5 cm. in thickness.

The dissecting aneurysm encircled the aorta in most of its parts with only occasional areas, where the lamellæ remained attached to each other. The blood clot in all portions of the dissecting aneurysm was dark red and friable in nature and of recent origin.

Anatomic Diagnosis. Rupture of the aorta; dissecting aneurysm of aorta; arteriosclerosis of coronary and cerebral arteries; softening of brain; and recurrent nephritis.

Résumé. A man, aged 38 years, suffering from Bright's disease and cerebral arteriosclerosis, died suddenly with no symptoms particularly referable to the heart. The Wassermann reaction was negative. The autopsy disclosed a transverse rupture of the descending thoracic aorta leading to a dissecting aneurysm extending from the heart to the iliac veins. Leakage from this aneurysm took place into the left pleural cavity. There were no lesions of the intima having any relation to the site of rupture. It is probable that the rupture of the aorta and the dissecting aneurysm occurred 15 days before his death. Further evidence of this was obtained on microscopic examination, when a well-established granulation tissue was found to clothe the inner wall of the dissecting aneurysm.

Microscopic Examination of the 5 Cases. To avoid undue repetition in the description of the microscopic characteristics in the aorta, the findings in the above 5 cases will be discussed conjointly. This is also desirable as the quality of the change observed in the aortic wall is similar in all cases, though it varied in its extent. In Cases 1 and 2 the lesions were particularly located in the ascending limb of the aorta, while in Cases 3, 4 and 5 the pathologic process in the middle coat of the aorta was to be seen throughout the length of this vessel.

The common characteristic of the arterial lesion lay in the presence of patchy or diffuse necroses in the media. For the most part this degenerative process occupied the zone between the middle and outer third of the media though at times it extended inwardly or outwardly into the neighboring zones. These necroses were unaccompanied by an inflammatory reaction, and they were devoid of a fibrosing process in their neighborhood. At the point of rupture there was no lesion of the intima which could serve as a localizing factor, but it was noted that the amount of necrosis in the underlying media was usually greater at this point than elsewhere.

In Cases 1 and 2 where the dissecting aneurysm remained localized to the region of the rupture, the necrotic process was present in patches which partly encircled the aortic wall, and extended to a varying length in a longitudinal direction. These necroses were bland in character and had led to the death of the muscle cells between several of the neighboring layers of elastic fibers. Occasionally the débris of the necrotic tissue remained at the site, but at other times the dissolution of the structure was more complete, leaving only a cleft filled with a colloid-like substance. At times the elastic fibers were spread apart by these small lakes of hyaline material, while at other times the degenerative process had also destroyed these fibers.

The flattened bands of necrosis and the cleftlike spaces in the media formed a procession of lesions encircling the aorta. In each case occasional areas were noted bordering upon the involved zone of the aorta, in which the muscle fibers showed a compensatory hypertrophy. This was more evident in the outer portion close to the adventitia. No direct relation could be established between the distribution of the vasa vasorum and the location of the necrotic process. In one instance the vasa vasorum were found with a moderate amount of endarteritis and a single arteriole showing an organized thrombus. In no instance was there a lesion of the aortic wall resembling syphilis or rheumatic fever.

Beside the degenerative changes in the muscle fibers there were also well-marked changes in the elastic laminae. Instead of running parallel courses about the circumference of the artery they were irregular in thickness, interrupted in their course, fragmented and often showing brushlike extremities at the termination of the elastic segments. The staining was variable, some fibers showing normal microchemical reactions, others appearing hyalin and jellylike in which the fibrils no longer showed normal staining qualities. The elastic fibers resembled those of old age, at times it was noted that they were very sparse in the vicinity of the vasa vasorum.

The path of the dissecting aneurysm followed the layer in the aorta in which the necroses were most extensive. This in our cases has most commonly been along the outer border of the middle third of the media. Occasionally the path would divert toward the adventitia or again toward the intima. On no occasion did the dissecting process enter the intima proper, and only in the regions where the external rupture of the aneurysm took place did the tear enter the adventitia. The wall of the dissecting aneurysm, made up of an inner and outer lamella of aortic tissue, showed a diffuse or patchy destruction of the media. In 2 cases a granulation tissue developed upon the torn surfaces with some organization of the blood in the aneurysmal sac, otherwise the immediate borders of the cavity were without reaction.

As previously indicated, the muscle fibers suffered more than the elastic fibers, and the extent of the destruction varied considerably. In some instances the aortic wall was not thinned, but the spaces intervening between the neighboring elastic lamellæ were filled with débris and fluid equal to the muscle tissues which had previously occupied the area. In the earliest stages of the degeneration, muscle fibers were found with altered nuclei or with remnants of nuclear material. Subsequently, the area became devoid of nuclear structures, while the cytoplasm of the cells resisted autolysis. These areas became acidophilic. A point worthy of comment is that in this series of cases there was an absence of the granular calcareous deposit which not uncommonly is found in the same zone in elderly people. This latter lesion, which we have previously described, represents a senile medial sclerosis of the aorta, analogous to Moenckeberg's sclerosis of the peripheral vessels. Under these conditions the elastic lamellæ are more closely compacted and thinning of the vessel wall takes place.

No unusual fatty changes were found in the middle coat of the aorta. Small clusters of granular fat were seen in groups of muscle fibers, but these were no more prominent than those found in individuals of this age.

A number of reactions secondary to the development of the dissecting aneurysm were also observed. It was noted that in the cases with extensive dissection of the aorta an edema developed in the intimal tissues and at times when life had been prolonged for some little time after the tear had occurred, a bordering strip of necrosis followed each side of the aneurysmal sac.

Discussion. In order to analyze the conditions in the aortic wall which are associated with spontaneous rupture, we have collected a series of cases from the literature, but have excluded all in which some demonstrable extraneous cause was apparent. Thus we have not included instances of infection and abscess formation in the aorta nor cases of exogenous tuberculous erosion which is at times observed in the thoracic aorta. Furthermore, as there are definite and peculiar changes arising in old age, quite different from the type lesion which is related to the occurrence of the tragedy in the younger individuals, the 42 cases of spontaneous rupture which we have collected from the literature, are limited to those individuals under 40 years of age. In none of these was there any evidence of an external factor, nor could it be shown that the rupture was related to an infectious process. It is of course evident, as we ourselves have encountered in 2 of the cases here reported, that the character of the lesion demonstrable in the aorta in individuals under 40 years may also appear in elderly individuals;

nevertheless, as some confusion may arise as to the actual tissue changes which may be encountered in aortic rupture in elderly individuals, we have omitted these from the present series. Erdheim and Gsell have both shown that the peculiar degenerative changes encountered in the media before middle life may be present in the cases of spontaneous rupture in individuals of advancing years. Cellina, on the other hand, points out that in elderly individuals, destructive changes in the muscle and elastic fibers are of several kinds, and that the specific quality of mucoid degeneration of the musculature is not the sole destructive lesion in the vessel.

The analysis of the cases collected from the literature appears in the following table:

TABLE 1.—RUPTURE OF AORTA (IN INDIVIDUALS UNDER 40 YEARS).
Number of cases, 42; males, 28; females, 14.

Ages:			
1 to 10			2
11 to 20			7
21 to 30			20
31 to 40			13
Interval to death:			
Immediate death			6
Hours interval (A few hours to 12 hours)			5
Days interval (1 day to 5 days)			7
Weeks interval (12 days to 5 weeks)			3
Not stated			21
	Present.	Absent.	Not stated.
Associated physical strain	12	26	4
Death sudden	40	1	1
Dissecting aneurysm	17	7	18
Rupture into pericardium	32	7	3
Arteriosclerosis of aorta	10	20	12
Syphilis (determined by Wassermann reaction)	1	13	28
Location of rupture:			
Ascending aorta			33
Arch			6
Thoracic aorta			1
Not stated			2

Spontaneous rupture of the aorta appears to occur twice as often in males as in females; and though it may appear in any decade of life, even in children under 10, it is more common in the later years. No explanation is evident to account for the higher incidence in the reported cases in the third decade over the fourth. Physical strain is a determining cause in a minority of the cases, and in no instance was it the important reason for the development of the peculiar aortic lesion found in these cases.

The onset of the rupture is usually accompanied by severe intrathoracic and radiating pain, while dyspnea and nausea commonly follow. Death does not always take place with the initial tear, as the rupture may penetrate only the inner coats of the arterial wall and not lead to complete rupture. Death may be delayed for a

period of weeks, and even, we believe, not take place as a result of the partial rupture; but the condition may continue to persist as a dissecting aneurysm which may, through granulation tissue, undergo healing. It is our interpretation that every dissecting aneurysm represents a partial rupture of the aorta, and that the conditions underlying the development of dissecting aneurysm are those found in spontaneous rupture of the aorta. This background upon which rupture of the aorta occurs is a peculiar degeneration of the media of the aorta, and is not associated with an antecedent inflammatory process. It is obvious from the evidence in our own cases, as well as from that of the literature, that syphilis plays no part in the production of spontaneous rupture nor in dissecting aneurysm. The very nature of the syphilitic process, with the development of connective-tissue bands in the aorta, precludes the splitting of the aortic wall into lamellæ as seen in both of these lesions.

In each of our 5 cases of spontaneous rupture of the aorta, there was evidence of some degree of dissecting aneurysm, although in 2 of them the condition remained localized to the vicinity of the tear, and might readily have been overlooked. This is particularly true in the younger individuals in whom the dissecting quality of the vessel wall is less pronounced, save at the very margin of the tear where the peculiar degenerative changes in the media are localized.

The greatest frequency of the tear in the aortic arch is determined by the medial degeneration which most often occurs with intensity in this region. With advancing years there is a tendency for the peculiar degenerative changes to become more widely distributed and to occupy a considerable extent of the aorta. We have observed a patchy distribution of this mucoid degeneration in both the thoracic and abdominal aorta, but the most advanced process, associated at times with a bland necrosis of the muscle tissue, is more common in the ascending aorta than in other regions. It is worthy of note that this peculiar destructive lesion of the aortic wall is also to be found in the peripheral arteries of the muscular type. In 1905 Freedman, working in Adami's laboratory, described a cyst of the carotid artery which in structure was similar to the changes which have been so fully described in the aorta by Erdheim, Gsell, Cellina and others. Furthermore, we have observed similar lesions in the renal, coronary and neck arteries in the above cases, in which a complete dissecting aneurysm occupied the aorta.

It is obvious, therefore, that lesions in the intima play no part in the occurrence or localization of the rupture unless, as in rare instances, an atheromatous excavation lies by chance immediately above the lesions in the media. In old age the site of rupture for the production of a dissecting aneurysm may bear a closer relation to the presence of atheromatous ulcers, inasmuch as the latter are not uncommonly associated with senile atrophies of the media which, though differing in their pathogenesis from the mucoid degen-

erations and necroses in younger individuals, give rise to a fragile structure permitting the development of dissecting processes.

There is little direct evidence available indicating the manner in which the medial necrosis makes its appearance. Those who have studied the condition are in agreement that the lesions do not arise through interference with the nutrition by way of the vasa vasorum. None have found thromboses or other occluding processes in these vessels of nutrition, although we have reported the presence in 1 case of an organizing thrombus in several nutrient arteries. In this instance, however, we were unable to relate this circulatory disturbance to the various necroses scattered through the aortic wall. Wiesel believed that the lesions in the media were the result of bacterial toxins, as he had encountered such degenerations in the vascular tissues of children dying of acute infectious diseases. In the absence of other indications, this suggestion was supported by Stoerck and Epstein, and by Gsell. Others contend that not only bacterial toxins, but also certain exogenous poisons (adrenalin, nicotine) and poisonous products of metabolism (renal toxins and liver products) may affect the arterial wall in a manner similar to bacterial toxins. None have been adequately demonstrated to affect the vessel wall in the peculiar manner as related above. Furthermore, the nature of the lesion obtained in animals by the use of adrenalin is not identical with the specific change, as seen in mucoid degeneration. Recently Duff, working in these laboratories, has shown us effects of diphtheria toxin on the media of experimental animals which are very similar to the patchy muscle destruction in man. Admitting that certain bacterial toxins may cause medial degenerations and necroses, it is far from clear how these processes become progressive and appear in their advanced form many years after the infectious process. Nor do the ruptures of the aorta appear only in those individuals who have suffered unusual frequency or severe grades of infectious diseases.

It is possible that certain dietary deficiencies play a part in the degeneration of the vascular musculature and that other super-added factors (toxins) intensify the effect; but it is too early to offer conclusive evidence upon these points. We are, however, of the opinion that the end results are due to a variety of factors and are not dependent upon the effect of one agent alone.

There is need for a thorough study of the degenerative lesions of the media, the recognition of the types and the mode of their development. These lesions are important in the subsequent outcome of clinically recognizable diseases which must not be confused with arteriosclerosis localized in the intima. In the past too little attention has been given to processes affecting the media alone or in which the intima has been involved in a secondary reaction.

Summary. 1. An analysis is given of 5 cases of so-called spontaneous rupture of the aorta.

2. A common underlying process was demonstrated in all cases, consisting of a peculiar noninflammatory degeneration of the media, affecting the muscle and elastic fibers, due to a variety of factors.

3. Similar lesions precede the development of dissecting aneurysms.

4. The peculiar medial degeneration is found, aside from spontaneous rupture or dissecting aneurysm, with increasing frequency with advancing age, either as a diffuse process or in sporadic distribution through the aorta.

5. The lesions have no relation to syphilis.

REFERENCES.

1. Babes, V., and Mironescu, Th.: *Beitr. z. path. Anat.*, 1910, 48, 221.
2. Bay, H.: *Frankf. Zeit. f. Path.*, 1911, 6, 70.
3. Cellina, M.: *Virchow's Arch. f. path. Anat.*, 1931, 280, 65.
4. Erdheim, J.: *Virchow's Arch. f. path. Anat.*, 1929, 273, 454.
5. Erdheim, J.: *Virchow's Arch. f. path. Anat.*, 1930, 276, 187.
6. Freedman, A.: *Montreal Med. J.*, 1909, 38, 583.
7. Gsell, O.: *Virchow's Arch. f. path. Anat.*, 1928, 270, 1.
8. Krukenberg, E.: *Beitr. z. path. Anat.*, 1920, 67, 329.
9. Oppenheim, F.: *München. med. Wehnschr.*, 1918, 65, 1234.
10. Oppenheimer, R.: *Virchow's Arch. f. path. Anat.*, 1905, 181, 382.
11. Rokitansky, C.: *Med. Jahrb. der K. K. Österr. Stattes*, 1838, 16, 24.
12. Robertson, H. F.: *Arch. Path.*, 1929, 8, 881.
13. Schnurbein, F.: *Frankf. Zeit. f. Path.*, 1926, 34, 532.
14. Stoerck, O., and Epstein, E.: *Frankf. Zeit. f. Path.*, 1920, 23, 163.
15. Wasastjerna, E.: *Zeit. f. klin. Med.*, 1903, 49, 405.
16. Wiesel, J.: *Zeit. f. Heilk.*, 1906, 27, 262.
17. Wiesel, J.: *Zeit. f. Heilk.*, 1907, 28, 69.
18. Woodruff, C. E.: *Am. J. Path.*, 1926, 2, 567.

THE HYPOTENSIVE ACTION OF POTASSIUM SULPHOCYANATE IN HYPERTENSION.*

BY ROBERT STERLING PALMER, M.D.,

ASSISTANT IN MEDICINE, MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL, BOSTON, AND ASSISTANT CARDIOLOGIST, BOSTON LYING-IN HOSPITAL.

(From the Medical Clinic of the Massachusetts General Hospital.)

THE literature on the pharmacology, the therapeutic effect and the by-effects of the sulphocyanates (thiocyanates, rhodan compounds) has been thoroughly reviewed.^{1,2,3} Favorable hypotensive effects have been reported, though a certain number of disagreeable by-effects have been encountered. Fineberg⁴ found a large dosage more effective, using 5 grains of the potassium salt for each dose instead of the usual 1½ grains. More recently Ayman⁵ and Egloff, Hoyt and O'Hare⁶ have reported their inability to use this drug in sufficient dosage to obtain the hypotensive action without producing

* The expense of this study was paid by a grant from the Proctor Fund for the study of chronic disease.

by-effects so unfavorable that the drug had to be given up. While it is true that the effective therapeutic dose of this drug is not far from the toxic dose for some individuals, nevertheless, in a certain proportion of cases the hypotensive action may be obtained without unduly disagreeable symptoms.

Method of Study. It is desirable to have certain criteria by which the presence or absence of a blood pressure lowering effect may be judged since the spontaneous variability of the blood pressure, even in the more advanced stages, is well known, while the favorable response to earnest therapeutic suggestion may be quite marked.⁷ In addition to the observations extending over a period of months to years the patients who were the subjects of this study were subjected to special observation, usually under a prescribed régime of diet and rest with or without simple sedatives such as bromids or barbital compounds. Some were given a regular dosage of plain peppermint water, while a few were given potassium sulphocyanate in peppermint water if there had been sufficiently frequent previous examinations during a trial course of some other drug supposed to have a hypotensive action. In all cases the attempt was made to obtain adequate preliminary control in addition to extended previous examinations by other observers.

To avoid the benefits of suggestion and to judge the hypotensive action of potassium sulphocyanate alone, this drug was prescribed in peppermint water in concentrations of $1\frac{1}{2}$ grains and of 5 grains per drachm. During subsequent control periods plain peppermint water was prescribed. These various preparations were prescribed by code and filled by the hospital apothecary. All were given without special suggestion, being alike referred to as for the blood pressure. The more salty taste of the stronger concentration could be recognized and was commented upon by one or two patients. In general, however, the effect of suggestion in these patients was avoided. Courses of 4 to 8 weeks with $1\frac{1}{2}$ grains of the drug 1 to 3 times daily, or 5 grains 1 to 3 times daily alternated with similar periods with plain peppermint water, 1 drachm 1 to 3 times daily. At each visit the patient was examined in the sitting position; the cuff was placed on the left arm (except in a one-armed patient and in one whose arterial circulation in the left arm had been interrupted). A mercury manometer was used; the same observer made the examination. In general the visits were as much alike as possible. Usually ten readings in as many minutes were made. The usual fall in successive readings, especially the later ones, was found in most cases; this is in part due to modification of the circulation below the cuff since changing the apparatus to the other arm will usually find the first pressures similar to the first pressures found with the cuff on the previous arm. However, the changes each time would be the same and it was felt that a possible effect due to relaxation of nervous tension would be obtained.

Material. Expecting that, should potassium sulphocyanate have an hypotensive action, one could obtain alternate rises and falls in the blood pressure of sufficient degree to be clear and definite, this drug was administered to 63 patients with persistent continued arterial hypertension. Twenty-two were discarded because of incomplete study or poor coöperation, and 5 were discarded because of fall in blood pressure apparently due to loss of weight, the use of bromids, or because of marked unaccountable variations in the blood pressure level before using potassium sulphocyanate.

Thirty-five patients remained in whom the therapeutic and toxic effects of potassium sulphocyanate were studied. Fifteen were males and 20 were females. Their ages by decades were as follows: 30 to 39 years inclusive, 4 patients; 40 to 49 years inclusive, 12 patients; 50 to 59 years inclusive, 15 patients; 60 to 69 years inclusive, 4 patients.

The exact duration of the hypertension was unknown in the majority of cases but was known to have existed for long periods up to 10 or more years in several patients. The majority showed at least some evidence of the late effects of continued arterial hypertension. Only 3 were diagnosed essential hypertension alone and 1 of these, a woman aged 35 years, showed arteriosclerosis of the aortic arch. Five had pure hypertensive heart disease and in 1 other this diagnosis was questioned. Twenty-five had "hypertensive and arteriosclerotic heart disease" and in 1 other this diagnosis was questioned. Other diagnoses included angina pectoris in 5, congestive heart failure and cardiac asthma in 4, hypertensive crises or hypertensive encephalopathy in 3, hypertension of the "malignant type" in 4, and carcinoma of the rectum successfully operated upon and without evidence of recurrence or metastasis in 1.

The eye grounds were examined in 22. Nine showed no definite abnormality. Thirteen showed various degrees of change from mild arteriolar sclerosis to marked hypertensive retinitis with hemorrhages and papilledema. Twenty-eight of these patients were studied fluoroscopically and by means of Roentgen ray plates with the tube at 7 feet. Nineteen of these 28 cases showed cardiac enlargement, 16 especially of the left ventricle. In 2 the enlargement was general and in 1 the shadow was rounded. Tortuosity of the aorta was present in 23 cases. This finding was accompanied by dilatation of the aorta as well in 5. The aorta was dilated without tortuosity in 1. Thus the majority of patients in this series gave evidence of structural changes, the result of or accompanying continued arterial hypertension.

Results. (a) *Hypotensive Action.* If, during administration of the drug, the blood pressure of the patient was definitely lower than when the drug was not given, if moreover the blood pressure rose when the drug was omitted and again fell when it was given, the hypotensive action was regarded as certain. Sometimes this cycle

was again repeated. Of the 35 cases studied 7 showed this undoubted hypotensive action. Chart I shows an effect considered certain.

If a similar though not so marked an effect was obtained or if the blood pressure was at first higher without the drug, then lower

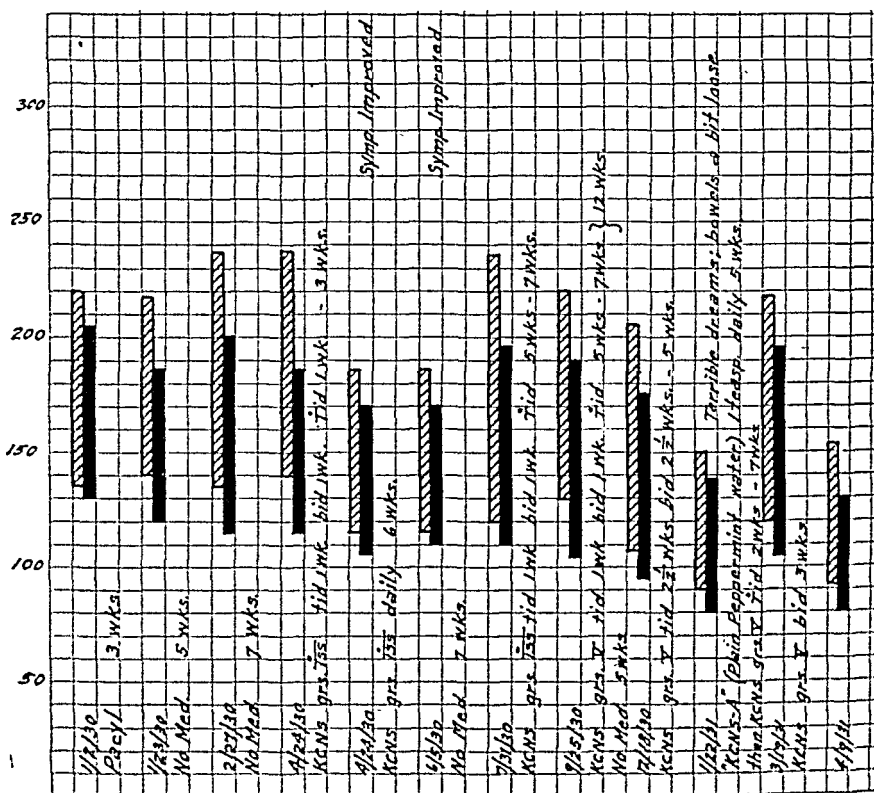


CHART I.—The effect of potassium sulphocyanate upon the blood pressure in a case of essential hypertension. Each abscissa marks off the blood pressure in millimeters of mercury as indicated. The cross-hatched columns represent the highest systolic and diastolic pressure and the solid columns represent the lowest systolic and diastolic pressure at each visit. Usually these columns indicate the upper and lower limits of ten readings. The time interval between visits is given in each case. This chart shows not only the lower levels of the blood pressure under the influence of potassium sulphocyanate but the less marked variation as well. While on the drug the blood pressure was down and while off the drug or while the drug was not taken continuously, as between Sept. 25, 1930 and December 18, 1930, the blood pressure was up. It is also seen from this chart that the effects obtained after the first fall in blood pressure required larger doses. This chart represents a certain hypotensive effect of potassium sulphocyanate.

with the drug, again higher without the drug, but on again giving the drug an hypotensive action was not clearly obtainable the result was regarded as probable. The second hypotensive effect usually was more difficult to obtain than the first. Four of the 35 patients showed a probable hypotensive action. Chart II illustrates

an effect regarded as probable. If the blood pressures fell when on the drug but did not exhibit the subsequent rise without it and another fall with it or if the variations were not as clear as in the probable reactions, the results were held to show possible hypotensive effects, as illustrated in Chart III. There were 13 such patients. Eleven failed to show any hypotensive action. Eleven (31.42 per cent) of this series of 35 patients exhibited either a certain or a probable hypotensive action of potassium sulphocyanate.

(b) *Dosage Required.* The dosage was varied considerably according to the ability of the patient to take the drug, but in general two

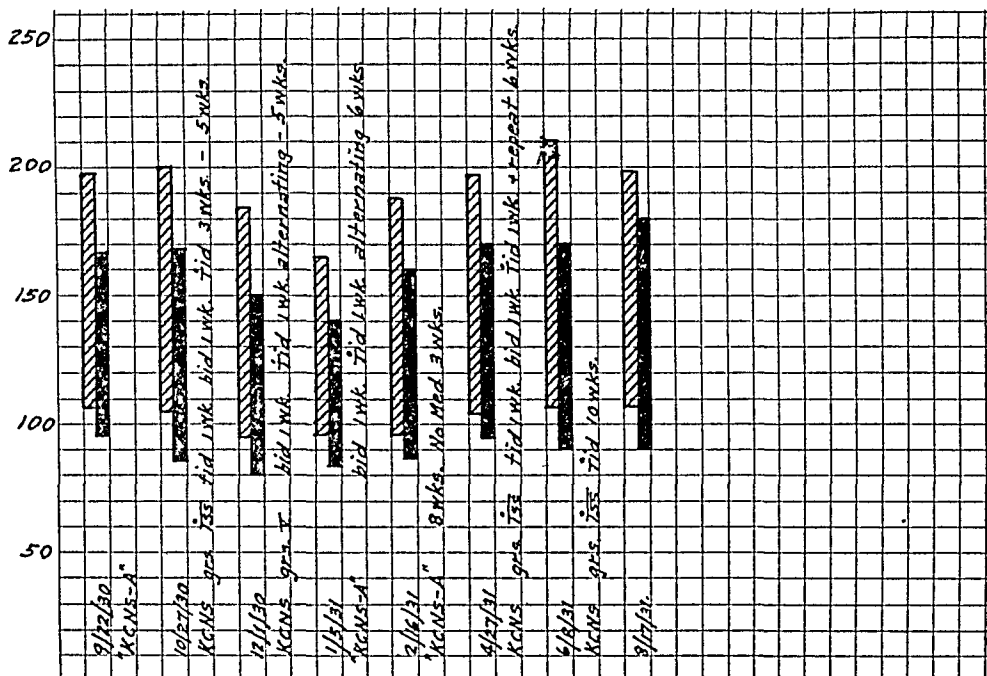


CHART II.—A probable hypotensive effect of potassium sulphocyanate. The result is not as clear as that shown in Chart I. In this case a second fall in the blood pressure under the influence of potassium sulphocyanate was not obtained, though it might have been had larger doses been used. The first fall under its influence, however, seemed to be very definite.

concentrations were employed, $1\frac{1}{2}$ grains per drachm and 5 grains per drachm of peppermint water. These doses were given from 1 to 3 times daily for 4 to 8 or 10 weeks. The weaker concentration only was used in 15 cases while both the weaker and stronger concentrations were used in 20, which included the 7 patients showing the certain effect and the 4 patients showing the probable effect. Only 4 patients in whom the stronger concentration was used failed to show at least a possible hypotensive effect.

(c) *By-effects.* In the 35 patients disagreeable by-effects were encountered 9 times and in 2 additional patients symptoms occurred

which may have been due to the drug, in 1 an acneiform rash and in the other a questionable increase in anginal pain and weakness, complaints which were present before the use of the drug. The symptoms definitely related to the drug in the 9 patients were as follows: increase in anginal pain once and onset of anginal pain once; general weakness twice; nightmares once; gastrointestinal symptoms once; nausea and feeling of nervousness once; vertigo with some mental confusion once; and a severe toxic psychosis once. In 6 cases the higher concentration of the drug was used. Weakness in 1 patient and angina pectoris in 2 cases resulted apparently from the smaller dosage.

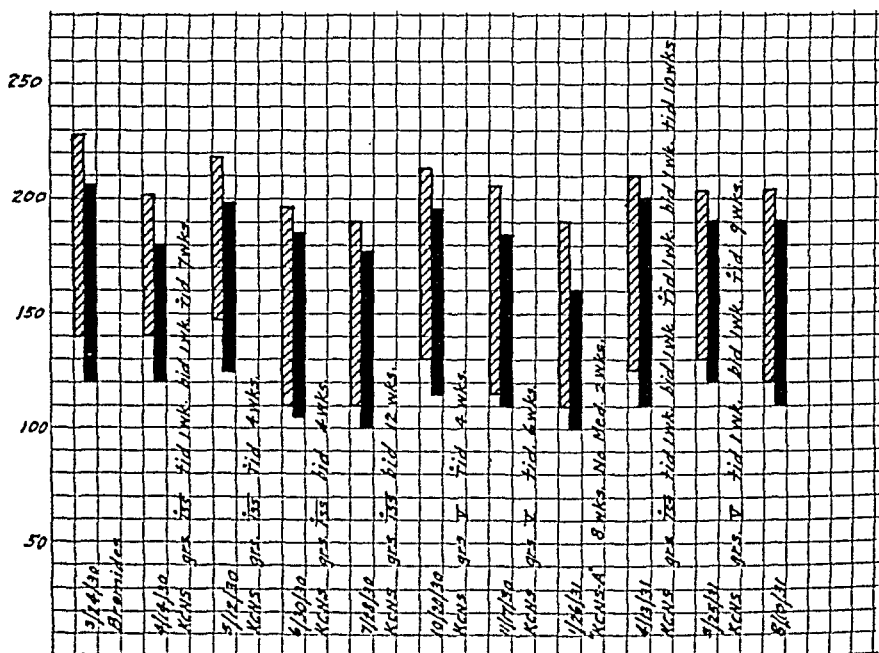


CHART III.—A possible hypotensive effect. There seemed to be a definite hypotensive action exerted by potassium sulphocyanate, though the effect was not as clear-cut as in the group of certain effects represented by Chart I.

Blotchy red measles-like rashes have been noted in 2 patients not in the present series, 1 the patient of a colleague and 1 a patient treated since study of this series was completed. In the first patient the rash appeared a week after taking 5 grains 3 times daily and in the other after a similar time on 1½ grains 3 times daily. Another patient reported to me by a colleague developed an acneiform rash similar to a bromid rash after 2 weeks' treatment.

Unaccountable nervousness with some nausea was complained of by 1 patient while taking 5 grains of the drug 3 times daily. With a similar dosage another experienced terrifying dreams. Two patients

not in this series (1 excluded because of too brief observation and 1 treated since completing this study), experienced acute attacks of excitement; mental confusion and apprehension in 1 lasted $\frac{1}{2}$ hour, in the other continued in a somewhat milder degree for 24 hours. The most marked nervous manifestation amounted to a true psychosis requiring admission to the Boston Psychopathic Hospital. This unfortunate result was accompanied by a fall in systolic pressure from a previous average for several weeks of 200 mm. of mercury systolic to 115 mm. systolic. A good recovery was made, after which the pressure again gradually rose to its former level. The patient volunteered that she felt better than she had for 2 years and was able to return to work.

Summary and Conclusions. Thirty-five well controlled patients, most of them showing the effects of continued arterial hypertension, have been treated by potassium sulphocyanate.

This drug when used in sufficient dosage caused a definite and marked lowering of the arterial blood pressure in 31 per cent of the patients.

Toxic effects are skin rashes, gastrointestinal symptoms and central nervous system symptoms, such as acute apprehension and excitement, which may be severe enough to constitute a toxic psychosis.

Weakness may accompany the use of the drug but is probably not a toxic effect and does not necessarily contraindicate its use. Angina pectoris, in those subject to this symptom, may be increased and in some patients may be induced by the use of this drug.

Toxic effects are reduced to the minimum by carefully controlled dosage.

Limited observation of the use of the drug in combination with a general régime including rest and diet suggests that it may be of value, though these results may not be referred to in accurately appraising the hypotensive action. Generally speaking it may be said that the hypotensive effect is not lasting and that a second or third such effect after the drug is once discontinued is more difficult to obtain.

BIBLIOGRAPHY.

1. Gager, L. T.: The Incidence and Management of Hypertension With a Note on Sulphocyanate Therapy, *J. Am. Med. Assn.*, 1928, **90**, 82.
2. Smith, A. G., and Rudolf, R. D.: The Use of Sulphocyanate of Soda in High Blood Pressure, *Can. Med. Assn. J.*, 1928, **19**, 288.
3. Palmer, R. S., Silver, L. S., and White, P. D.: The Clinical Use of Potassium Sulphocyanate in Hypertension, *New Eng. J. Med.*, 1929, **201**, 709.
4. Fineberg, M. H.: Potassium Thiocyanate in the Treatment of Patients With Hypertension, *J. Am. Med. Assn.*, 1930, **94**, 1822.
5. Ayman, David: Potassium Thiocyanate in the Treatment of Essential Hypertension, Its Impracticability, *J. Am. Med. Assn.*, 1931, **96**, 1852.
6. Egloff, W. C., Hoyt, L. H., and O'Hare, J. P.: Observations on Thiocyanate Therapy in Hypertension, *J. Am. Med. Assn.*, 1931, **96**, 1941.
7. Ayman, David: An Evaluation of the Therapeutic Results in Hypertension. II. The Interpretation of Blood Pressure Reductions, *J. Am. Med. Assn.*, 1931, **96**, 2091.

HARMFUL EFFECTS OF NITROGLYCERIN.

WITH SPECIAL REFERENCE TO CORONARY THROMBOSIS.

BY SAMUEL H. PRODGER, M.D.,

INSTRUCTOR IN MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL,

AND

DAVID AYMAN, M.D.,

ASSISTANT IN MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL.

(From the Medical Clinic of the Boston Dispensary, Dr. J. H. Pratt, Physician-in-Chief, and the Department of Medicine, Tufts Medical School.)

NITROGLYCERIN is generally considered a drug in no way dangerous to prescribe, and it is usually administered without any particularly careful observation or supervision. However, in the course of recent studies in which therapeutic doses of nitroglycerin were given to 110 patients under direct observation, we observed alarming reactions to the drug in 4 instances. The reactions in the 4 patients were similar in many respects. In each case there was a rapid and marked drop in blood pressure, and the pulse rate was greatly diminished. Severe constitutional symptoms developed in all 4 patients, consisting chiefly of cold perspiration, weakness, restlessness, anxiety, and pallor. Each patient presented a picture of impending collapse. The blood pressure of 2 patients became so low that it could not be recorded, and the pulse could not be felt. The rapid fall in the blood pressure of another patient apparently was checked by the quick administration of epinephrin. Complete heart block developed in 1 case; in another case the course of coronary thrombosis was thought to be unfavorably influenced.

Literature.—Toxic reactions to therapeutic doses of nitroglycerin have received little mention in the literature. The older writers seem to have been more cognizant of these harmful effects of nitroglycerin than modern writers. Shortly after the drug was established as a therapeutic agent by Sobrero¹ in 1847, there appeared several articles pointing out the dangers of the drug. Honert,² Field,³ and Noer⁴ reported toxic reactions to therapeutic doses of the drug. In Honert's patient unconsciousness developed; Field, taking the drug himself, was observed to become pulseless; in Noer's patient there was great prostration, cold clammy perspiration, slow and heavy breathing, and a very slow and irregular pulse following the administration of the drug. Loeb,⁵ in 1908, reported severe collapse which resulted from as little as $\frac{1}{10}$ grain (0.5 mg.) of nitroglycerin.

Several authors have mentioned contraindications and dangers in the use of nitroglycerin without giving specific evidence or case reports. Cornwall⁶ mentioned various contraindications to its use

and simply stated that it should not be given to patients "who have any idiosyncrasy in regard to its actions." Peterson, Haines and Webster⁷ stated: "In most of the fatal cases a large amount of the poison was taken but it seems probable that a few drops would prove fatal." According to Sollmann⁸ even small doses may cause alarming syncope and cardiac slowing.

Recently White⁹ called attention to 2 patients who collapsed with syncopal attacks after taking $\frac{1}{100}$ grain (0.65 mg.) of nitroglycerin. In the recent American literature one is impressed by the fact that there exists, with rare exception, a general disregard for the possible harmful effects of nitroglycerin. Perhaps as a result of this there has developed a rather widespread unrestrained use of the drug in all conditions involving spasm of involuntary muscle.

Since we observed reactions in a relatively high proportion (almost 4 per cent) of our cases following therapeutic doses of nitroglycerin, and because these reactions were of a serious character, we consider the subject of sufficient clinical importance to be worthy of emphasis.

Our 4 patients were women between the ages of 58 and 67 years. In 1 patient the diagnosis of angina pectoris was definite; in all 4 patients there was arterial hypertension. In each patient before giving the drug we made repeated determinations of the blood pressure until a resting level was reached. Therefore, the changes in the blood pressure following the administration of the nitroglycerin may be regarded as due to the effect of the drug. In addition the blood pressure was frequently determined during and after the administration of the nitroglycerin. In 2 of the patients several electrocardiograms were obtained during the reactions.

Case Reports. CASE 1.—A woman, aged 67 years, entered the clinic March 15, 1930, complaining of nervousness, weakness and pains in the joints of her hands. These symptoms had begun 9 months previously following a mild accident when a window fell on her right hand. Since then she had also suffered from vertigo, occasional palpitation of the heart on exertion, moderate shortness of breath on climbing one flight of stairs, loss of energy, and slight swelling of the finger joints of the right hand with severe sharp pain in them.

Physical examination disclosed Heberden's nodes on the fingers of both hands. The heart was not enlarged, its sounds were distant, the rate was 80, and the rhythm was regular. The blood pressure was systolic 190 and diastolic 90. The radial arteries were slightly thickened with some beading. Examination of the ocular fundi showed moderate narrowing of the arterioles. The urine was free of albumin, and contained 30 hyalin casts in 10 low-power fields. The Hinton test for syphilis was doubtful. The patient did not return for 2 months because when blood was drawn for the Hinton test at the first visit she fainted and had been apprehensive about returning. On the second visit the blood pressure was systolic 158, diastolic 78. An orthodiagram showed the heart to be of normal size. An electrocardiogram (Fig. 1) showed sinus rhythm, a rate of 70, a *P-R* interval of 0.17 second, a *Q-R-S* interval of 0.07 second, the *T* wave in Lead 1 erect and low, the *T* wave in Lead 2 slightly inverted, the *T* wave in Lead 3 diphasic, and left axis deviation.

Chart I and Fig. 1 show the blood pressure and electrocardiographic changes which occurred during the administration sublingually of a pill containing $\frac{3}{16}$ grain (1.3 mg.) of nitroglycerin. The blood pressure dropped in 10 minutes to an indeterminate point. The pulse became very slow and finally not palpable. Pallor, weakness, a cold clammy sweat, restlessness, anxiety and faintness developed. The patient did not lose consciousness. Epinephrin (0.5 cc. of a 1 to 1000 solution) was given intramuscularly. Five minutes later the blood pressure and pulse still could not be determined. Then the blood pressure rose rapidly; in the next 2 minutes it had reached a level of systolic 154, diastolic 80. During the entire period of observation eight electrocardiograms were taken. These showed, among other things, the development of complete heart block.

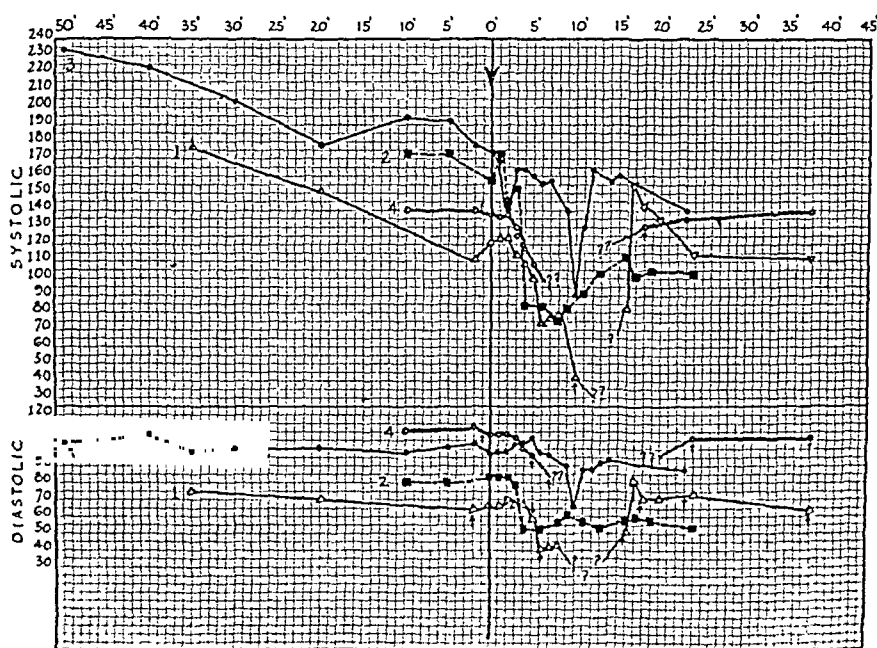


CHART I.—The blood pressure readings of the 4 cases reported; the upper curves represent the systolic, and the lower curves indicate the diastolic pressure. Where the blood pressure became indeterminate, the curve is broken by question marks. To the left of the vertical line at O' are minutes before, and to the right of this line, minutes after the administration of the nitroglycerin. Small arrows indicate times when electrocardiograms were taken.

CASE 2.—A woman, aged 58 years, had been coming to the clinic for 17 years complaining at various times of pains in the knees, back and thorax, and of light-headedness, shortness of breath, poor appetite, occasional swelling of the legs, occasional headache, faint feeling in the stomach, pain around the heart, sleeping poorly, tiring easily, vomiting, nervousness, numbness in the right ear, and lack of energy.

Physical examination on various occasions disclosed moderate varicosities of the right leg, very slight pitting edema of the ankles, a soft systolic murmur over the apical region of the heart, and slight hypertrophic changes in the terminal joints of the fingers and in both knee joints. During the last 4½ years arterial hypertension had been present. In January, 1927,

the blood pressure was systolic 205, diastolic 110; in January, 1928, it was systolic 175, diastolic 110.

On November 13, 1930, the patient was given $\frac{1}{100}$ grain (0.65 mg.) nitroglycerin (1 drop of freshly opened spirits of nitroglycerin). The effect on the blood pressure is shown in Chart I. Within $3\frac{1}{2}$ minutes the blood pressure dropped from systolic 172, diastolic 84, to systolic 82, diastolic 52. The patient began to feel generally weak, light-headed, restless and nau-

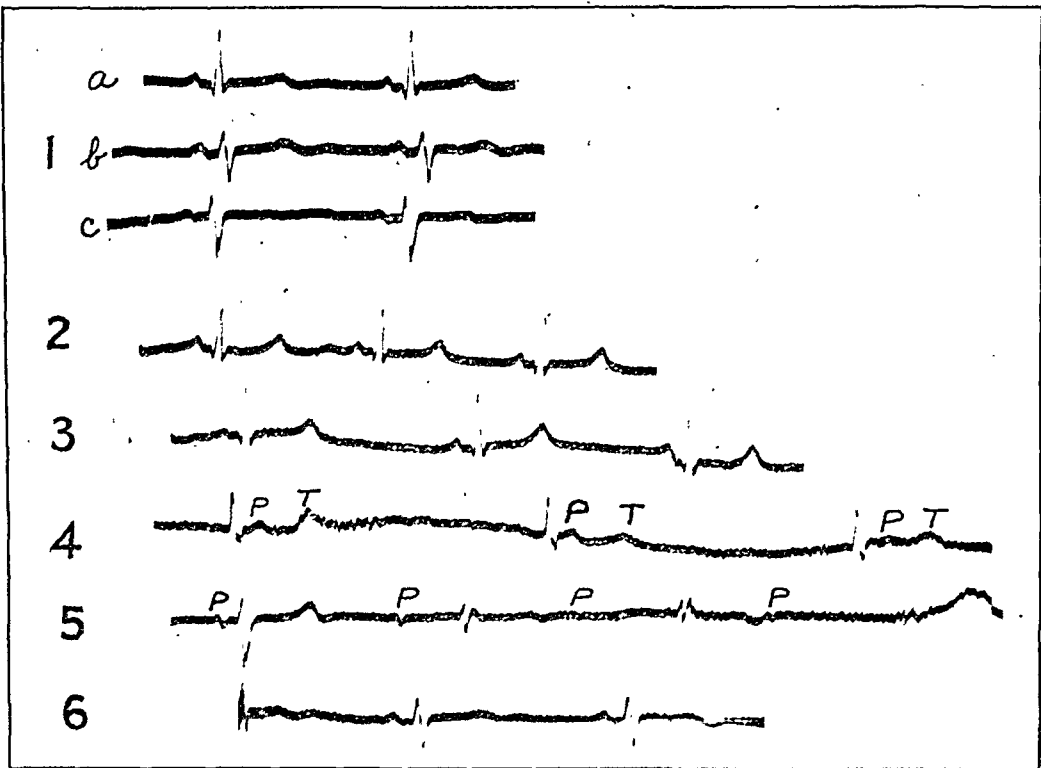


FIG. 1.—Electrocardiogram number 1: *a*, *b*, and *c* are Leads 1, 2, and 3 respectively. This electrocardiogram was taken 2 minutes before $\frac{1}{100}$ grain nitroglycerin was given. . . . Electrocardiogram number 2 shows Lead 1, 5 minutes after $\frac{1}{100}$ grain nitroglycerin; the heart rate has increased from 82 to 95 per minute. . . . Electrocardiogram number 3 shows Lead 1, 6 minutes after the nitroglycerin, rate 66. . . . Electrocardiogram number 4 shows Lead 1, 10 minutes after the drug; nodal rhythm, rate 47. . . . Electrocardiogram number 5 shows Lead 3, 16 minutes after nitroglycerin, showing complete heart block; the *P* waves are inverted indicating probable retrograde conduction; auricular rate 65, ventricular rate 50; note general diminution in voltage; this is probably not due to position change of the heart associated with respiration, as the breathing at this time was no different than when electrocardiogram number 4 was taken, when no such changes were observed in Lead 3; it is likely that the marked diminution in voltage was associated with the collapse and weak heart action.

Horizontally 1 cm. = 0.35 sec.; vertically 1 cm. = 1.25 millivolt.

seated. She became pale and cool to the touch, and perspired freely. The pulse became very slow and feeble; the rate was 44 a minute. At once 8 minims of epinephrin (1 to 1000) was given subcutaneously, and this dose was repeated in 3 minutes. Twenty-six minutes later the blood pressure still was only systolic 100, diastolic 58, and the patient looked and felt very ill. Sixty-five minutes after the injection of epinephrin the blood pressure had risen only to systolic 136, diastolic 56. The patient has been observed

in the clinic since then up to the present time, and no permanent ill effect of the nitroglycerin has been observed. She has continued to have arterial hypertension.

An electrocardiogram taken one week after the nitroglycerin was given did not show abnormalities. An orthodiagram taken 1 week afterward showed the heart to be of normal size and shape. Study of the ocular fundi, April 13, 1931, showed markedly narrowed arteries and considerable arteriovenous compression. The response to the dilution and concentration tests of renal function was normal.

CASE 3.—A woman, aged 64 years, had been observed in the clinic for 2½ years, and had had essential arteriolar hypertension during this period. She had known that she had hypertension for 3 years before coming to the clinic. She had had occasional spells of tiring easily, light-headedness, and dull headaches, but in general had had comparatively few symptoms. When she first came to the clinic she complained of shortness of breath on climbing two flights of stairs, but this disappeared in a few weeks under the administration of bromids.

Physical examination and a teleroentgenogram showed slight enlargement of the heart to the left. Examination of the fundi showed markedly narrowed arterioles, moderately engorged veins, and numerous old and fresh retinal hemorrhages throughout. The response to tests of renal function was normal, with the kidney able to concentrate urine up to a specific gravity of 1.025. The Hinton and Wassermann tests were negative. The systolic blood pressure varied on many visits between 252 and 150, and the diastolic between 130 and 88.

Chart I shows the reaction to the sublingual administration of 1/50 grain (1.3 mg.) nitroglycerin (2 drops of spirits of nitroglycerin). Within 9 minutes the blood pressure dropped from a resting level of 178 systolic, 98 diastolic, to 90 systolic, 66 diastolic. The patient said she felt tired and weak. She appeared pale and anxious. The pulse rate was 48. The blood pressure, however, quickly and spontaneously rose. The patient felt weak for 1½ hours after taking the drug. An electrocardiogram a few weeks after the nitroglycerin was taken did not show abnormalities.

CASE 4.—A woman, aged 63 years, was first seen September 7, 1931, complaining of pains in the thorax which had been present for about 1 year. She had had a total of about 50 attacks of the same description. The pain was situated under the middle of the sternum over an area about 10 cm. in diameter, and when very intense it was also present in both forearms. The sensation was described "as if something were expanding" in the thorax. It lasted 2 to 3 minutes and then subsided. There was no difficulty in breathing when the pain was present. Following the attacks there were eructations of gas. At no time was there shortness of breath. During the last year the pain had been brought on occasionally by walking up two flights of stairs, but in the 3 days before the patient was first seen it had been induced by the mild exertion of the minor duties of housework. The pain had been more severe during these 3 days, and the patient had been forced to stop immediately when it came on. Two nights previous to examination in the clinic the pain had waked the patient out of a sound sleep. The family history showed that the patient's father had died at the age of 63 of "angina pectoris." A sister had arterial hypertension.

Following the excitement and exertion of undressing for the examination the patient stated that she was having an attack of pain. The blood pressure was then systolic 218, diastolic 140. Eight minutes later the pain had disappeared and the blood pressure was systolic 194, diastolic 128. The important points in the physical examination were as follows: the skin was slightly dry; moderate arteriovenous nicking in the fundus oculi was present; cardiac impulse was felt in the fifth interspace 12 cm. to the left

of the midsternal line, with a powerful impulse over an area the size of three finger tips; the cardiac measurements on percussion were 12 cm. to the left and 5 cm. to the right of the midsternal line; there were no thrills; the heart sounds were of fair quality, with no weakness of the first sound, rate of 95 and regular rhythm; there were no murmurs and no friction rub; the pulse was of good quality; the radial arteries were soft, and edema was not present.

Nitroglycerin in a dose of $\frac{1}{16}$ grain (0.43 mg.) was prescribed for the pain. The next morning the patient stated that she had taken one nitroglycerin pill the night before with moderate relief of the pain. She had not experienced headache, faintness or other discomfort following the nitroglycerin, but she had felt a quivering sensation over the heart. At 9 A.M. the pulse rate was 92, and the blood pressure was systolic 160, diastolic 118. On the same day at 1 P.M., after a half hour's rest reclining, the blood pressure was systolic 136, diastolic 108. The patient felt and looked well. At this time she was given sublingually a nitroglycerin pill containing $\frac{1}{16}$ grain. In 6 minutes the blood pressure had dropped to an indeterminable level, and the pulse was not palpable. The patient became anxious, restless, pale, cold, moist with perspiration, and nauseated. Three subcutaneous injections of epinephrin (0.4 cc. each of a 1 to 1000 solution) were administered over a period of 12 minutes. During these 12 minutes the blood pressure and pulse were unobtainable and the patient appeared to be in a state of collapse. Then the blood pressure gradually rose to its resting level (Chart I). The patient vomited once. A few minutes later she complained of slight pain in both forearms, probably brought on by the epinephrin.¹⁰ This subsided after she lay quietly for a few minutes. The patient was able to return home in a taxi. Some of the electrocardiograms taken during this period are shown in Fig. 2.

The patient was not seen again until 4 days later, at her home. She stated that since the reaction from the nitroglycerin she had felt very weak, and had had inconstant nausea. She had not experienced pain or shortness of breath, but she was barely able to get around her home because of weakness. She looked pale. Her skin was cool and moist. Her pulse was thin and regular, and the rate was 92. The blood pressure was systolic 80, diastolic 70. The heart still had a forceful impulse although the impulse was more easily compressible than when palpated on the first visit to the clinic. There was a marked systolic thrill localized at the apex. A very loud blowing systolic murmur was present at the apex. The measurements of the heart were unchanged. The sounds were of fair quality; the rate was 90 and the rhythm was regular. The aortic second sound was equal in intensity to the pulmonic second sound. There was no pericardial rub. The edge of the liver was not felt. The respirations were shallow and regular, and the rate was 38 a minute. Examination of the lungs was negative. The temperature was 97° F. by mouth, and 98° F. by rectum. The white blood count was 12,300, and the differential count was normal. The specific gravity of the urine was 1.030. The urine contained the slightest possible trace of albumin when tested with heat and acetic acid. Sugar was not present. The patient was at once put to bed and treated for coronary occlusion. She was seen repeatedly during the next few days. The blood pressure remained at the same low level. A state of circulatory collapse continued for 6 days, and death occurred from bronchopneumonia.

Comment. In Case 1, about 10 minutes after the administration of $\frac{1}{16}$ grain (1.3 mg.) of nitroglycerin the blood pressure had dropped to a point at which it could no longer be determined, the pulse could not be felt, and complete heart block developed. We are fortunate in having, in addition to frequent readings of blood

pressure, eight electrocardiographic tracings taken before and during the course of the reaction. The electrocardiograms showed first a slight increase in pulse rate, which is common following nitroglycerin. In succession, sinus bradycardia, atrioventricular nodal rhythm, and finally complete heart block (atrioventricular dissociation) were revealed by the electrocardiograms (Fig. 1). With the return of the blood pressure to a normal level following the administration of epinephrin, the heart block disappeared and normal sinus rhythm was reestablished. An electrocardiogram taken several months later showed no evidence of heart block. The significance of the slight *T* wave changes following the administration of nitroglycerin is to be considered in a later paper.¹¹ So far as we know there have been no cases in human beings reported which show such definite intracardiac conduction changes following the administration of nitroglycerin.

In connection with the reaction which the patient in Case 1 exhibited, several factors are to be considered. There was a spontaneous drop in the blood pressure over a resting period of 35 minutes before nitroglycerin was given, from a level of systolic 176, diastolic 74, to systolic 120, diastolic 66. In view of this large drop and the previous variations of the blood pressure as indicated in the case report, it is evident that labile hypertension was present. Whether the lability was in any way related to the unusual response which followed the administration of the nitroglycerin it is difficult to say. It may be mentioned that many of our patients with a similar lability of blood pressure did not show such a response to the drug.

Another factor to be considered as possibly related to the unusual response to nitroglycerin in Case 1 is the type of patient, namely an emotionally unstable woman who had been known to have attacks of syncope in response to excitement. It is hardly likely in this case that the great lowering of blood pressure and the development of bradycardia and heart block were due to excitement on the part of the patient, inasmuch as she had had two previous electrocardiographic studies and was apparently perfectly at ease when the nitroglycerin was administered. This state of emotional relaxation was also indicated by the drop in blood pressure during the 35 minute period of rest prior to the administration of the nitroglycerin. Such drops in blood pressure are common phenomena and usually indicate emotional relaxation in labile arteriolar hypertension.¹² When electrocardiograms were taken several months later under similar conditions, at which time sodium chlorid instead of nitroglycerin was administered sublingually, no change in the electrocardiogram, pulse or blood pressure was observed. This also would make it seem unlikely that excitement attending the administration sublingually of the drug could have been responsible for the reaction. The fact remains that in this case of an emotional patient with labile hypertension a therapeutic dose of nitroglycerin produced an

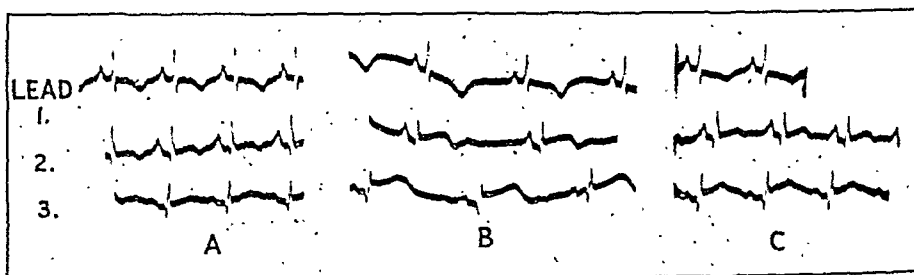
acute, alarming and dangerous reaction. It should be noted, however, that in this case, as in Case 3, a dose of $\frac{1}{50}$ grain (1.3 mg.) of nitroglycerin instead of the more usual dose of $\frac{1}{100}$ grain (0.64 mg.) was given. Whether or not these severe reactions would have been avoided had only $\frac{1}{100}$ grain (0.64 mg.) been given it is impossible to state.

In Cases 2 and 3 the drop in blood pressure was marked, but not beyond determination. Similarly the pulse became slow and weak, but it was always palpable. Subjectively the reactions were similar to the reactions in Case 1 in that there were weakness, vertigo, intense anxiety, restlessness and a sense of approaching unconsciousness. In neither case did unconsciousness supervene. In Case 2 the drop in blood pressure was apparently checked by the administration of epinephrin in two successive doses of 0.5 cc. each of a 1 to 1000 solution. In Case 3 the blood pressure spontaneously rose rapidly after it had dropped from systolic 178, diastolic 98, to systolic 90, diastolic 66. Unfortunately no electrocardiographic tracings were obtained during the reactions in Cases 2 and 3.

In Case 4, although we did not realize it at the outset, in retrospect it is evident that we were dealing at the time of the administration of nitroglycerin with slowly developing, painless cardiac infarction. At this time, although the resting blood pressure level was as low as systolic 138, diastolic 108, we did not appreciate its significance as the patient had no complaints and felt able to perform customary activities. However, the blood pressure the day before the administration of nitroglycerin was systolic 190, diastolic 128. This fact, together with the clinical course following the administration of the nitroglycerin, indicates that at the time the nitroglycerin was administered the cardiac infarction was probably developing. With the administration of $\frac{1}{100}$ grain (0.64 mg.) of nitroglycerin, the blood pressure dropped in 5 minutes from a resting level of systolic 138, diastolic 108, to a point at which it no longer could be determined. At this time the pulse was not palpable. The alarming aspects of the reaction are further indicated in the case report. The question now naturally arises: Did the nitroglycerin contribute to the fatal outcome of the case? Hadfield¹³ pointed out that the size of a cardiac infarction is increased when the blood pressure is lowered artificially. Hubble¹⁴ emphasized the danger of using nitroglycerin in coronary thrombosis on the basis of the work of Hadfield and others, and thought that this danger makes it important to distinguish clearly between simple angina pectoris and cardiac infarction. In the American literature, on the other hand, nitroglycerin is considered of such little danger in coronary thrombosis that it is frequently advocated as a means of distinguishing between angina pectoris and cardiac infarction. Levine,¹⁵ White,⁹ Eggleston¹⁶ and Gorham,¹⁷ among others, simply stated that nitroglycerin is of no value in coronary thrombosis and indicated its differential diagnostic

value in the latter disease and angina pectoris. The possible dangerous effects are rarely mentioned, and as a result there is in general little or no hesitation in giving nitroglycerin when a patient is suspected of having coronary thrombosis.

In Case 4 the electrocardiogram taken immediately before the administration of nitroglycerin showed evidence of coronary disease. The electrocardiograms taken at the time when the pulse could not be felt and before epinephrin was given showed sinus bradycardia with marked exaggeration of the *T* waves in all leads (Fig. 2). There was no evidence of disturbance of intracardiac conduction. There was, however, definite evidence of increasing cardiac ischemia. In Lead 3, for example, the take-off of the *T* wave becomes distinctly higher while the *S-T* interval in Lead 2 becomes more characteristically "coronary" in type. These changes



Horizontally 1 cm. = 0.35 sec.; vertically 1 cm. = 1.25 millivolt.

FIG. 2.—A, Leads 1, 2, and 3, 1 minute before $\frac{1}{10}$ grain nitroglycerin was given under the tongue; B, Leads 1, 2, and 3, 7 minutes after the nitroglycerin; note the slowing of the rate, the exaggeration of the *T* waves, the more definite cove-shaped appearance of the *T* wave in Lead 2 and the higher take-off of the *T* wave in Lead 3; C, Leads 1, 2, and 3, 38 minutes after the nitroglycerin (three doses of epinephrin, minims 6 each, had been given between B and C). *T* waves have not completely returned to original appearance although blood pressure had been at starting level for fifteen minutes.

are very similar to those which Feil, Katz, Moore and Scott¹⁸ observed when, after ligation of the left coronary artery in dogs, they lowered the blood pressure artificially by temporarily occluding the inferior vena cava. In their experiments and in Case 1 reported here, it appears that the mere lowering of the blood pressure did not produce myocardial ischemia. It was only when there was some coronary occlusion, as in Case 4, that lowering of the blood pressure produced these ischemic changes. The fact that the patient's condition became suddenly and rapidly worse immediately following the taking of the nitroglycerin indicates causal relationship since such a quick marked effect could hardly have been coincidental. The clinical events, combined with the electrocardiographic changes, indicate that nitroglycerin is distinctly harmful in coronary thrombosis. Other recent clinical experiences tend to confirm this view.¹⁹ The observations of Luten²⁰ suggest that nitroglycerin, by lowering

the diastolic blood pressure, may even serve as a contributory factor in precipitating coronary thrombosis in any case of coronary sclerosis.*

The lowering of blood pressure, absence of palpable pulse, and extreme faintness almost to the point of unconsciousness may of themselves be of no particular significance. They may represent simply a transient exaggerated reaction to nitroglycerin, the type of reaction that one frequently sees following the administration of amyl nitrite, for example. The fact is significant, however, that following the administration of nitroglycerin heart block developed in 1 case, and a probably harmful effect on the course of cardiac infarction was observed in another. Common to all 4 cases was a definite slowing of the pulse rate as evidence of toxicity.²¹

The mere fact that patients do not complain of unusual symptoms following the taking of the drug is not an indication that they have not experienced a toxic or unusual reaction. For example, when the patient in Case 1 was questioned after the reaction from nitroglycerin was over, she stated that she had been disturbed chiefly by a feeling of faintness, which is not an unusual sensation following the taking of nitrites. The patient in Case 4 complained after the reaction from nitroglycerin only that it seemed a little close in the room and that she simply wanted for air. Had these 2 patients taken the drug at home unsupervised, they would probably have reported to their physician little or no ill effects.

As a result of our experiences we have made it a rule in both hospital and private practice never to give nitroglycerin for the first time to patients without personal supervision, and observation of the blood pressure and pulse. Usually a small initial dose is given ($\frac{1}{200}$ to $\frac{1}{300}$ grain). Epinephrin is kept readily available. When the response to the drug is normal we feel safe in allowing the patient to take the drug at home. In the rare cases† in which toxic reactions do occur, indicating idiosyncrasy to the drug, it is of course not prescribed.

The harmful effects of nitroglycerin may be easily overlooked in coronary thrombosis; for, this is a disease of grave prognosis and the ill effects of therapy are with difficulty separated from the frequent

* P. D. White has recently observed a patient who, when given $\frac{1}{100}$ grain nitroglycerin to relieve the pain of angina pectoris, developed a syncopal attack which came with the relief of pain. When the patient recovered from the syncopal attack in the course of 15 to 20 minutes his pain came back and he went through the typical illness of coronary thrombosis for which he was in the hospital for several weeks. White feels that, while it is possible that the attack of pain for which he gave the patient nitroglycerin was actually the beginning of coronary thrombosis, it is also quite likely that the attack was one of angina pectoris and that the reaction to nitroglycerin favored the production of coronary thrombosis. White suggests using $\frac{1}{200}$ to $\frac{1}{400}$ grain (0.32 to 0.16 mg.) of nitroglycerin as an initial dose. (Personal communication to the authors.)

† P. D. White, who has given nitroglycerin to more than 500 patients with angina pectoris, knows of bad effects only in 2 cases. (Personal communication to the authors.)

spontaneous fatal terminations. It would seem advisable that patients with angina pectoris who are taking nitroglycerin for the relief of pain should be carefully observed, and at the earliest indication of coronary thrombosis administration of the drug should be stopped. When nitroglycerin is given unwittingly in a case which proves to be coronary thrombosis, careful observations should establish further its possible harmful effects.

Summary and Conclusions. 1. Nitroglycerin in therapeutic doses was administered to 110 patients under direct observation. Alarming toxic reactions were observed in 4 cases. In two instances the blood pressure became indeterminable and the pulse could not be palpated. Heart block developed in one of these, and in the other the course of a cardiac infarction was thought to be unfavorably influenced. A record was made of the electrocardiographic changes which occurred during the reactions in these 2 cases. In the other 2 cases there were, as evidence of toxicity, marked slowing of the pulse rate, great drop in blood pressure, and severe constitutional symptoms.

2. Careful supervision of the patient is advised when the first dose of nitroglycerin is administered, in order that those who have an idiosyncrasy to it may be discovered and possible dangerous reactions avoided. A small initial dose ($\frac{2}{100}$ to $\frac{3}{100}$ grain) is advised.

3. The possible harmful effects of nitroglycerin in coronary thrombosis are indicated.

BIBLIOGRAPHY.

1. Sobrero, A.: *Compt. rend.*, 1847, 24, 147. Quoted in *Schmidt's Jahrb.*, 1867, 134, 346.
2. Honert: *Ein Fall von Vergiftung durch Nitroglycerin*, *Deutsch. Klin.*, 1867, 19, 83.
3. Field, A. G.: *Toxic and Medical Properties of Nitroglycerin*, *Med. Times and Gaz.*, 1858, 37, 291. Quoted in *Schmidt's Jahrb.*, 1867, 133, 350.
4. Noer, J.: *Poisonous Symptoms from Nitroglycerin*, *Therap. Gaz.*, 1887, 3, 459.
5. Loeb, A.: *Klinische Untersuchungen über den Einfluss von Kreislaufsänderungen auf die Urinzusammensetzung*, *Deutsch. Arch. f. klin. Med.*, 1905, 83, 452. Quoted by Miller, J. L.: *J. Am. Med. Assn.*, 1910, 54, 1666.
6. Cornwall, E. E.: *When and How to Use Nitroglycerin*, *J. Am. Med. Assn.*, 1913, 61, 118.
7. Peterson, F., Haines, W. S., and Webster, R. W.: *Legal Medicine and Toxicology*, Ed. 2, Philadelphia, W. B. Saunders Company, 1923, 2, 672.
8. Sollmann, T.: *A Manual of Pharmacology*, Philadelphia, W. B. Saunders Company, 1917, p. 380.
9. White, P. D.: *The Significance and Treatment of Cardiac Symptoms*, *New Eng. J. Med.*, 1931, 205, 907.
10. Levine, S. A., Ernestene, A. C., and Jacobson, B. M.: *Use of Epinephrin as a Diagnostic Test for Angina Pectoris*, *Arch. Int. Med.*, 1930, 45, 191.
11. Prodger, S. H.: *The Effects of Nitroglycerin on the T wave of the Human Electrocardiogram*. (To be published.)
12. Ayman, David: *Normal Blood Pressure in Essential Hypertension*, *J. Am. Med. Assn.*, 1930, 94, 1214.
13. Hadfield, G.: *Discussion of Cardiac Infarction*, *Lancet*, 1928, 1, 189.
14. Hubble, D.: *Angina Pectoris and Coronary Disease*, *Lancet*, 1930, 1, 908.
15. Levine, S. A.: *Coronary Thrombosis; its Various Clinical Features*, *Medical Monographs*, Baltimore, The Williams & Wilkins Company, 1929.
16. Eggleston, C.: In *Cecil's Text-book of Medicine*, Philadelphia, W. B. Saunders Company, 1930, p. 1069.

17. Gorham, L. W.: In Blumer's Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, 2, 595.
18. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, *Am. Heart J.*, 1931, 6, 522.
19. Levine, S. A.: Personal Communication to the Authors.
20. Luten, D.: Contributory Factors in Coronary Occlusion, *Am. Heart J.*, 1931, 7, 36.
21. Cushny, A. R.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1924, p. 402.

NEUROBLASTOMA OF THE ADRENAL WITH MULTIPLE METASTASES.

BY JACOB KLEIN, M.D.,

INSTRUCTOR, DEPARTMENT OF PEDIATRICS, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO.

(From the Department of Pediatrics, Northwestern University Medical School.)

NEUROBLASTOMA of the adrenal is a rare type of tumor originating in the medulla of the gland, which is a part of the chromaffin system and develops in connection with the sympathetic nervous system. According to Wiesel¹ the termination of embryonal life does not necessarily signify completion of evolution of the medulla of the adrenal, but on the contrary the medulla is almost exclusively a product of postembryonal development and contains neuroblasts up to and even beyond the period of puberty. The comparative rarity of the tumor is indicated by Saphir's² report in which it was found to occur once in 3950 autopsies. Although Virchow³ was the first to mention the possibility of nerve tissue origin of such tumors his opinions were merely conjectural. Marchand,⁴ in 1891, was the first to recognize the tumor as originating in the nervous system and was the first to describe malignant tumors derived from fetal sympathetic ganglia. Roussy⁵ notes that the ganglion cells of the sympathetic nervous system are analogous to the cells of the central nervous system, having intraprotoplasmic granulations and neurofibrils just like the neurones. He states that sympathomas are often malignant tumors which metastasize throughout the body like cancer. The site of origin may be the suprarenal glands or the paravertebral ganglia, but the early extension of the tumor frequently renders the localization of the primary nodule difficult. The tumors are soft, frequently hemorrhagic and consist histologically of small cells with oval nuclei and very small amount of cytoplasm. The cells are arranged either in a diffuse network or in rosettes on a supporting reticulum consisting of connective tissue and neurofibrillæ. Wollstein,⁶ in her very interesting series, notes that although the majority of reported tumors of this type have been found in or grown from the adrenal medulla, they may grow

from embryonal sympathetic cells or sympathicoblasts anywhere in the body. In 1910 Wright⁷ used the term "neuroblastoma" and brought about a general acceptance of the belief in the neuroblastic origin of the growth.

Clinically the growth may manifest itself as the type described by Pepper⁸ with pronounced visceral and liver metastases or as the Hutchinson⁹ type with secondary growths in the long bones, skull, sternum and vertebræ. Frequently postorbital metastases occur and may cause a protrusion of the eyeball and a confusion with chloroma. The tumor of the adrenal is usually encapsulated and does not tend to invade directly the surrounding organs. Extension occurs usually through lymphatics and bloodvessels.

In view of the rarity and the interesting features it is thought worth while to add the following case to the literature on this subject:

Case Abstract.—J. M., a girl, aged 2½ years, was admitted to Sarah Morris Hospital, February 26, 1931, complaining of pain, swelling of the knees and ankles, difficulty in walking, marked pallor, anorexia, abdominal pains and marked night sweats, particularly about the head.

She had appeared to be entirely well until 7 weeks prior to the admission when she began to have pains and swellings in the joints of both legs associated with difficulty in walking, which persisted for the past seven weeks. During the 2 weeks prior to admission a swelling had been noticed on the right side of the face at the angle of the jaw. The mother had noticed a progressive increase in the pallor, considerable dyspnea during the day, as well as occasional abdominal pain. She had loss of appetite with considerable loss in weight.

She was born about 2 weeks prematurely, delivered normally and weighed 5½ pounds at birth. The static development was normal; at 1 year she weighed 21 pounds.

The father and mother are living and well. Another child, 3½ years of age, is in apparent good health. There was no family history of tuberculosis, malignancy or hereditary disease. No history of miscarriages.

On admission the child was very pale, weak and in poor general condition. She was not in pain, but seemed rather distressed and dyspneic. There was a firm, fixed swelling the size of a hickory nut attached to the right lower jaw in front of the ear. There was an ecchymosis on the left upper eyelid, although there was no protrusion of the eyeball. The pupils were equal and reacted to light and accommodation. No abnormalities were noted in the mouth, nose or ears. There was a moderate enlargement of the cervical glands.

The lungs were apparently normal. There was a loud systolic murmur over the aortic and mitral areas and no thrill. The abdomen was markedly distended. The liver extended 4 fingerbreadths below the costal margin. The spleen was not palpable. The superficial veins on the abdomen and thorax were quite distended. The extremities were thin and emaciated.

Blood Examination. February 27, 1931: Hemoglobin, 45 per cent; red blood cells, 1,250,000; white blood cells, 8,000. Differential count: Polymorphonuclears, 31 per cent; lymphocytes, 58 per cent; mononuclears, 5 per cent; myelocytes, 6 per cent.

March 21: Hemoglobin, 40 per cent; red blood cells, 1,300,000; white blood cells, 15,200. Differential: Polymorphonuclears, 43 per cent; lymphocytes, 47 per cent; mononuclears, 6 per cent; myelocytes, 4 per

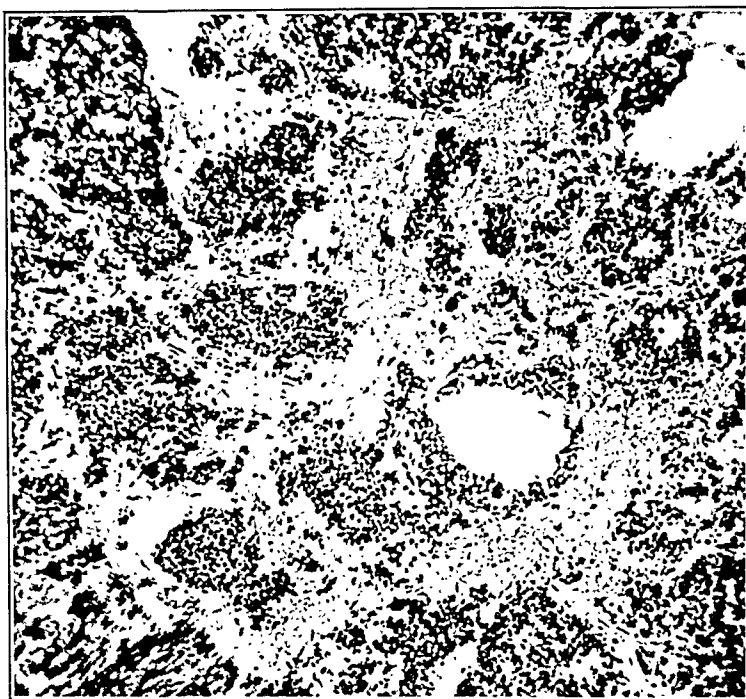


FIG. 1.—Photomicrograph showing "rosettes" of tumor cells.

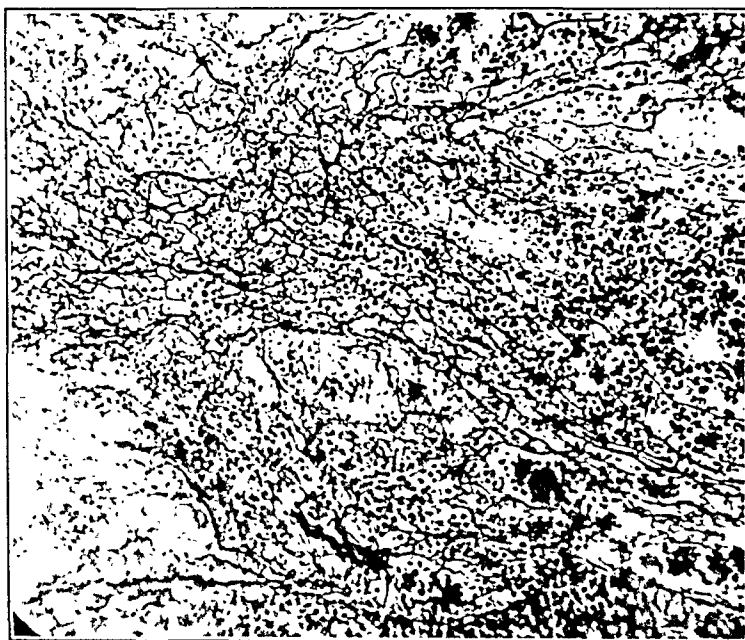


FIG. 2.—Pielchowsky stain showing neurofibrillæ.



cent. The blood Wassermann test was negative. Fragility test: Complete hemolysis, 0.36 per cent NaCl. Beginning hemolysis, 0.42 per cent NaCl. The urine was normal. The test for Bence-Jones albumose was negative.

Roentgen ray examination revealed a pathologic fracture of the right humerus just below the upper epiphysis. There was marked erosion of the left humerus in the same region. There was beginning destruction of the distal end of the left ulna. Practically all of the long bones showed periosteal proliferation and elevation. From the Roentgen ray examination the identity of the pathologic process was not clear. Although there were no characteristic findings a malignant growth was suspected.

The following diagnoses were considered: (1) Osteitis fibrosa cystica with sarcomatous degeneration; (2) sarcoma of the jaw with metastases to other bones and to the liver; (3) malignancy in some abdominal organ with metastases to the liver; (4) chloroma.

Because of the pronounced anemia a transfusion of 200 cc. of citrated blood was given soon after admission. However, there was no favorable response and the child became progressively worse. Soon there was ecchymosis over both eyes. The temperature rose to 105°. The child died a week after admission to the hospital.

Autopsy Abstract. (Dr. O. Saphir.) The body is that of a well-developed, anemic white girl, aged 2½ years. The eyes protrude and there is a hemorrhagic discoloration of the skin over both orbits. There is a firm fixed swelling in the region of angle of the right mandible, anterior to the ear.

The heart shows no abnormalities. There are a few firm areas in the right upper pulmonary lobe, which on cut section are bluish black in color and exhibit a tendency to confluence. The liver is markedly enlarged, reaching into the pelvis, and is studded with many small reddish-blue nodules. The spleen is slightly enlarged and rather firm. The surface shows several reddish nodules similar to those found in the liver.

The right kidney is compressed by a tumor which occupies the place of the right adrenal gland. The genito-urinary tract shows no other abnormalities. The left adrenal is apparently normal. The right adrenal is replaced by an encapsulated tumor which measures 3 by 5 cm. It is soft in consistency and on cut section consists of a dark reddish, in some parts almost black-looking material, which is finely granular in appearance. In the upper portion of the tumor there is seen a large, bright yellow area of necrosis which measures 0.5 by 2 cm. In some portions the capsule is yellowish, resembling the color of a normal cortex of the suprarenal. The tumor has pushed the liver downward and produced a marked depression of the right lobe with pronounced atrophy of this portion of the liver. There are many lymph nodes in the vicinity of the right adrenal which are invaded by the tumor. The aorta in this region is entirely encircled by the tumor nodes. The inferior vena cava in the region of the suprarenal vein shows a thrombus which extends into the suprarenal vein.

The mesenteric nodes and some of the lymph nodes at the mesenteric attachment are invaded by the tumor. The gastrointestinal tract shows no noteworthy changes.

In many portions of the calvarium there is diffuse involvement by the tumor tissue, which occurs in the form of nodules between the calvarium and the dura. Both orbital regions are invaded by the tumor. The brain shows no gross changes.

The osteochondral junction of the ribs shows tumor metastasis into the periosteum. There is a pathologic fracture in the neck of the right humerus. The line of fracture shows a large amount of the reddish-gray tumor tissue.

Microscopically the tumor consists of small round cells with dark staining nuclei. The cells are arranged in groups some of which show necrosis in

the center. The cells surrounding these necrotic areas assume the forms of pseudorosettes. (Fig. 1.) Other areas of the tumor show much necrosis and diffuse hemorrhage in the midst of which only few nuclei were recognizable. Sections stained by Bielschowsky's method reveal many dark fibers throughout the tumor. (Fig. 2.) Sections stained by Hortege's method and by Mallory's glial stain showed glial fibers throughout the tumor. The liver, spleen, lymph nodes and lung were invaded by the same tumor cells.

Pathologic Diagnosis. Primary sympatheticoblastoma of the right suprarenal medulla with metastases to the lymph nodes, calvarium, the left humerus, ribs, orbital fat tissue, liver, lungs and spleen. Pathologic fracture of the left humerus.

Summary.—1. A case of neuroblastoma or medulloblastoma of the right suprarenal gland in a girl, aged $2\frac{1}{2}$ years, is reported.

2. There was extensive visceral involvement (Pepper type) combined with numerous metastases in the lymph nodes, calvarium, humerus, ribs, orbital fat tissue, liver, lungs and spleen.

BIBLIOGRAPHY.

1. Wiesel, J.: Bemerkungen über Gliome der Nebennieren, Virchow's Arch. f. path. Anat., 1905, 180, 553.
2. Saphir, O.: Congenital Sympathicoblastoma of the Suprarenal, Arch. Path. 1927, 4, 207.
3. Virchow, R.: Die Krankhaften Geschwülste, Berlin, 1864.
4. Marchand, F.: Beitrag zur Kenntniss der normalen und pathologischen Anatomie der Glandulae Carotidæ und der Nebennier, Intern. Beitr. z. Wissensch. Med., 1891, 1, 578.
5. Roussy, G.: Le Cancer, Masson et Cie, 1929, p. 318.
6. Wollstein, M.: Neuroblastoma of the Adrenal in Young Children, Surg., Gynec. and Obst., 1928, 46, 774.
7. Wright, J.: Neurocytoma or Neuroblastoma: A Kind of Tumor Not Generally Recognized, J. Exp. Med., 1910, 12, 556.
8. Pepper, W.: Congenital Sarcoma of the Liver and Suprarenal, Am. J. Med. Sci., 1901, 121, 287.
9. Hutchinson, R.: Suprarenal Sarcoma with Metastases to the Skull, Quart. J. Med., 1907, 1, 33.

HYPOGLYCEMIA ASSOCIATED WITH A TUMOR OF THE ISLANDS OF LANGERHANS AND WITH ADRENAL INSUFFICIENCY, RESPECTIVELY.

BY JACOB RABINOVITCH, B.Sc., M.D., C.M.,

INSTRUCTOR IN PATHOLOGY, WASHINGTON UNIVERSITY MEDICAL SCHOOL, AND
ATTENDING PATHOLOGIST, MISSOURI BAPTIST HOSPITAL,

AND

FRANK W. BARDEN, B.S., M.D.,

INTERN, MISSOURI BAPTIST HOSPITAL,
ST. LOUIS, MO.

(From the Department of Internal Medicine of the Missouri Baptist Hospital, and the Department of Pathology of Washington University.)

THE occurrence of hypoglycemia in association with tumors of the islands of Langerhans, or as a result of various endocrine gland disturbances, has lately been well described. Many clinical reports

have appeared in the literature, together with much discussion of the nature of such hypoglycemic conditions. The results of these various observations have seemed sufficiently striking and inter-related to justify the conclusion that the primary factors responsible for the changes in the blood-sugar level are caused either by failure of the liver activities in liberating sugar, or because of overfunction of the pancreas in producing abnormal amounts of insulin. In addition to this it has been pointed out that certain functional disturbances of some of the endocrine glands, such as the thyroid, pituitary and adrenals, may also play a part in causing carbohydrate imbalance in the blood.

Great reductions in the sugar content of the blood have been observed to follow a variety of liver dysfunctions. In all such cases it has been shown that there exists either some faulty mobilization of the sugar, or inadequate storage function of the liver. Such liver dysfunctions are known to arise as a result of certain hepatic diseases, notably in chloroform, phosphorus, hydrazin and arsenic poisoning. Of great interest in this connection is the finding by Nadler and Wolfer¹ of a marked hypoglycemia in association with a widespread carcinoma of the liver.

Of particular interest to us is the part played by the adrenal glands in the causation of hypoglycemia. Unfortunately, the evidence for regarding the adrenals as the chief offenders in causing blood-sugar disturbances is very limited, and in many cases of doubtful significance. We might safely say, that a great deal of our knowledge concerning the rôle played by the adrenals in carbohydrate metabolism is deduced by analogy. Thus, it is well known that the administration of adrenalin will raise the blood sugar and is therefore used to abort hypoglycemic attacks. Also in Addison's disease, where the adrenals have been to a large part destroyed, a condition of hypoglycemia usually develops. Pettersson² reports a case of a patient who showed a hypoglycemia of 25 mg. per 100 cc. of blood, and autopsy revealed atrophy of the adrenals and thyroid with enlargement of the pancreas. So too, Anderson³ reports a case of a tumor of the adrenal gland which produced a fatal hypoglycemia. Just what part the adrenals play in the maintenance of the blood-sugar level is difficult to say, and all the various hypotheses which have been set forth to explain their manner of action are still of a speculative character. Experimental evidence points to the fact, however, that when extracts of these glands are administered to animals, there follows a definite rise in their blood-sugar level.

Hypoglycemic conditions with all the accompanying symptoms of hunger, sweating, nervousness, muscular twitchings, convulsions and coma have also been observed to occur in cases of cyclic vomiting, particularly in children. In many of these cases the blood sugar has been reduced to an exceedingly low level, and the administration

of large amounts of glucose to these patients has promptly relieved the condition. The exact mechanism concerned in bringing about such a hypoglycemic state is still obscure and not definitely determined.

Perhaps the most striking types of hypoglycemia have been noted in individuals in whom a tumor of the islands of Langerhans has been found. The occurrence of hypoglycemia in association with such tumors indicates the possibility of local incitation with increased insulin production. Wilder, Allan, Power and Robertson⁴ have shown that such an increased insulin formation could very well result from a carcinoma of the islands of Langerhans. Thalhimier and Murphey⁵ have also reported a case of carcinoma of the islands of Langerhans with hyperinsulinism and hypoglycemia. In the case of McClenahan and Norris⁶ an adenoma of the islands of the pancreas was found to be the cause of hypoglycemia. Howland, Campbell, Maltby and Robinson⁷ are perhaps the first to report a case of an islet tumor of the pancreas where removal resulted in a cure of the hypoglycemia. More recently, Carr, Parker, Groves, Fisher and Larimore⁸ and Womack, Gnagi and Graham⁹ have reported a case of an adenoma of the islands of Langerhans associated with hypoglycemia. In each of these 2 cases the condition has been diagnosed clinically and surgical removal of the tumor effected a complete cure of the patient.

The occurrence of hypoglycemia in conjunction with an islet cell tumor of the pancreas constitutes a powerful support to the contention expressed by many investigators, that the tumor is the causative agent for the hypoglycemia and the resulting clinical symptoms. It is very surprising to note that, in many of these cases, the tumor found in the pancreas is of unusually small size, and it is rather inconceivable that such a tiny tumor should account for the hyperinsulinism and the resulting hypoglycemia. It seems, then, that other factors must enter to explain the hypoglycemia on the basis of a pure hyperinsulinemia sequent to such a tumor. It is suggested, therefore, that in addition to the quantitative excess of insulin produced by an island tumor, there must be also a qualitative change in the character of such a secretion, insofar as it is much more potent than the normal substance regularly secreted by the normal islands of Langerhans. It is very difficult to state definitely, however, at this present state of our knowledge what are the abnormal qualities of this insulin or insulin-like substance that is elaborated by an islet tumor, and all the various theories which have been set forth to explain its atypical behavior are merely speculative in nature and not soundly founded.

It is of interest to note in this connection, that the majority of patients who develop attacks of hypoglycemia as a result of an islet-cell tumor are very rarely accurately diagnosed, although the clinical picture which they exhibit is quite unique and typical of hyper-

insulinemia. The neurologic symptoms which these patients present are very often confusing and are therefore misinterpreted. The condition is thus very frequently diagnosed as some disease process of the central nervous system such as epilepsy, syphilis, and others. We are inclined to believe that the infrequency with which these cases are reported is due not so much to their rarity, but rather to the inaccurate diagnosis that is being made. We might also add, that rather little attention has hitherto been paid to this phase of the problem, although we feel that the condition is sufficiently frequent to arouse greater interest.

During the last year 2 cases of hypoglycemia have come to our attention at the Missouri Baptist Hospital.

Case Abstracts. CASE 1.—This case has already been reported by Smith and Seibel;¹⁰ it is Case 4 of their paper. Briefly summarized, this case concerns an elderly white man who entered the hospital because of symptoms of vomiting and abdominal pains. He was operated upon for intestinal obstruction but at operation no obstruction was found; instead, the gall bladder was found filled with stones. The patient died 48 hours after the operation and at autopsy, performed immediately after death, a tumor of the islands of Langerhans was incidentally discovered. Dr. Bensley was able to demonstrate beta granules in these tumor cells by his special technique, but unfortunately these slides have not been preserved. Additional history obtained from the family following the discovery of the pancreatic tumor revealed the fact that the patient was subject to frequent attacks of amnesia and that he consumed unusually large amounts of sugar and sweetened food. There were also periods in which he seemed mentally confused and said strange things, and that such attacks were almost always relieved when fed with sweet food. Because of the above symptoms the family considered the patient as mentally deficient. Although no blood-sugar determinations were made in this patient, yet we felt quite confident, chiefly because of the typical clinical symptoms which he presented, that we were dealing here with a case of hypoglycemia caused by the pancreatic tumor. Furthermore, the cytologic studies made of this tumor revealed changes that were identical with those described in other cases, and in which the patients have been shown to suffer from hypoglycemia.

The second case is of particular interest because it differs from all other cases heretofore reported in the literature insofar as the primary cause of the hypoglycemia was an unusual lesion in the adrenals. This case will therefore be reported in some detail.

CASE 2.—C. S., a white male, aged 20 years, was admitted to the Missouri Baptist Hospital on July 11, 1931, in a state of stupor and semicoma. The history obtained from the family stated that he was apparently well until 2 months prior to his admission to the hospital. At that time the family first began to note in him a change in personality; he became despondent and melancholic and would not eat for several days at a time. He was married and his wife was pregnant; as a result of the general economic depression he was unemployed. The family therefore attributed his psychic state to the above adverse circumstances, and no particular attention was paid to his peculiar reactions. His general condition, however, became gradually worse and he began losing weight and complained of frequent

headaches. It was also noted at that time that he was consuming excessive amounts of sugar and sweetened food, and that the latter was out of proportion to his normal dietary intake. The patient claimed that he felt considerably better after eating sweets and was also more alert. Because of the progressive loss of weight and increased melancholia, the patient was sent to the country where he could rest. He felt somewhat better during the first day of his stay there, but on the following day he became very sick at his stomach and later lapsed into coma. He was then brought back to town and admitted to the hospital for observation.

On admission to the hospital the patient was stuporous and could be aroused only with difficulty. On physical examination nothing abnormal was found excepting that his right arm showed spastic contraction and was held in a position of external rotation. Within a very short period after entry to the hospital, the stupor deepened and the patient finally lapsed into complete coma. While in coma he was completely relaxed and the spasticity of the right arm had entirely disappeared.

Because of the very typical history which the patient presented, the condition was diagnosed at once as hypoglycemia, probably due to a tumor of the islands of Langerhans. A blood-sugar determination made of the patient shortly after his admission to the hospital showed a hypoglycemia of 25 mg. per 100 cc. of blood. Treatment was instituted immediately and large amounts of glucose were given intravenously. It was noted that in the course of the administration of the glucose the patient rallied, he began to regain consciousness and recognize the people that were standing around him. He became comatose again when the glucose was discontinued. The beneficial effects of the glucose upon the patient added support to our assumption that we were dealing with a case of hypoglycemia. This was corroborated by several blood-sugar determinations, all of which showed a very marked reduction in blood sugar. The glycemia continued at a very low level in spite of the constant administration of intravenous glucose. The patient finally lapsed into complete coma and failed to regain consciousness until his death, 48 hours later. Very shortly before death the blood sugar rose to 70 mg. per 100 cc. of blood.

An autopsy was performed within an hour after death. Our main attention at the time of autopsy was directed to the pancreas, since we felt quite certain that we were most probably dealing here with a case of hyperinsulinemia caused by a tumor of the islands of Langerhans. Examination of the pancreas disclosed a circumscribed and well defined nodule situated over the anterior surface and tail-end portion of the pancreas. This nodule was sharply demarcated from the surrounding pancreatic tissue. It measured about 5 mm. in diameter, was slightly raised from the surface and had a grayish discolored appearance. On cut section it appeared to extend for a distance of about 3 mm. into the depth of the pancreas. The cut surface of this nodule did not seem to have the same gross characteristics as was noted in the tumor nodule of our first case, but because of its striking differentiation and the absence of all other gross changes in the pancreas, it was anatomically diagnosed as an adenoma of the island tissue. The peri-pancreatic lymph nodes were somewhat larger and more prominent than normal.

The anatomic examination of all the other organs in the body failed to reveal any gross lesion, and these require therefore no further comment.

The microscopic examination of the nodule recovered from the pancreas disclosed rather unexpected findings. Instead of the suspected tumor of the islands of Langerhans, this nodule was found to consist of a localized area of chronic inflammation. There was not the slightest evidence of any neoplasm being present. In this inflammatory zone there were found isolated, but rather normal islands of Langerhans together with old remnants



FIG. 1.—Case 2. Photomicrograph showing the lesion in the adrenal. The cortex is of normal appearance, while the medulla is replaced by lymphoid tissue, the latter consisting of lymph follicles and scattered lymphocytes. ($\times 90$.)

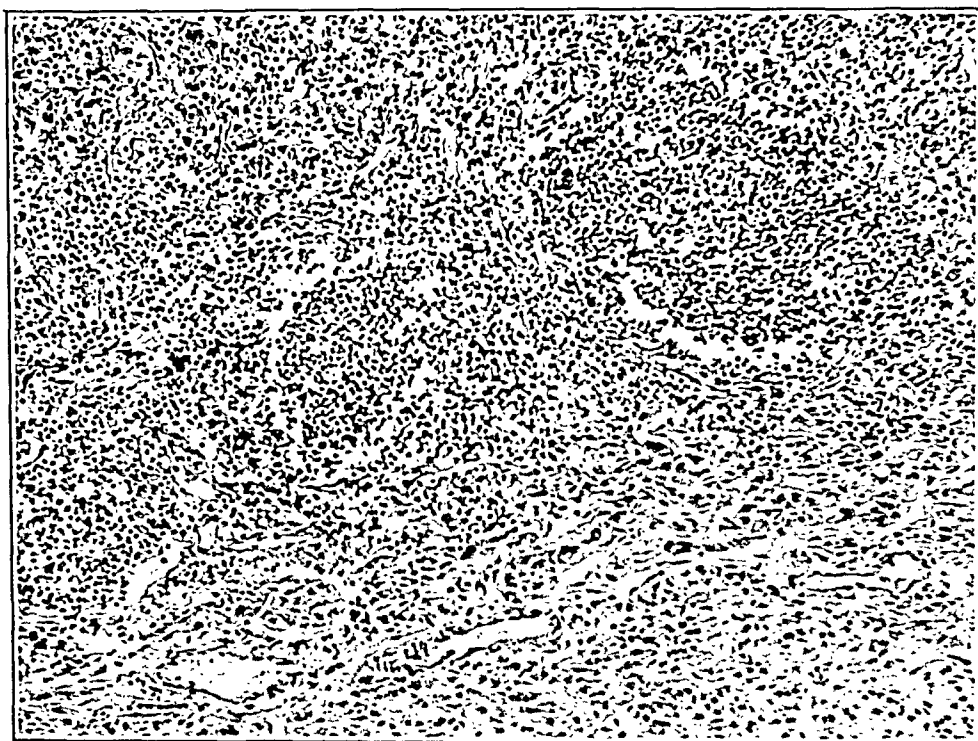


FIG. 2.—Same as Fig. 1 but a higher magnification. ($\times 150$.)

of gland and duct tissue. The stroma consisted here of diffuse fibroblastic proliferation with abundant lymphocytic and other inflammatory cell infiltration. Other portions of the pancreas showed similar inflammatory changes but to a very much less marked degree. The failure to identify this nodule as an adenoma of the island tissue prompted us to search the rest of the pancreas for any possible growth which might have been overlooked at the time of autopsy. The entire pancreas was therefore cut into very thin sections and every suspicious area was examined microscopically. No evidence of any tumor growth could be found in the entire pancreas.

Microscopic examination of the various other organs did not show anything abnormal excepting for certain unusual changes in the adrenals to be described below. The changes noted in these glands were identically the same in each organ and require therefore no separate description. The cortex of the adrenals was destroyed in places, while in others it still maintained its normal architecture and cell outline. The medulla, however, was entirely replaced by lymphoid tissue which was arranged in the form of distinct nests of lymphocytes surrounding a central collection of reticulo-endothelial cells. These nestlike structures had all the histologic appearances of lymph follicles, except for the fact that there was no well defined germinal center as is commonly observed in typically constructed lymph follicles. In the spaces between the various lymphocytic nests there was found a diffuse infiltration of lymphocytes and occasional giant cells. These giant cells were regarded as foreign-body cells and not associated with any tuberculous lesion. In addition to the lymphocytes and giant cells, there were also noted scattered in the medulla old remnants of desquamated medullary tissue. No evidence of any normal medullary tissue could be distinguished anywhere in the various sections studied. (Figs. 1 and 2.)

The replacement of the medullary portion of the adrenals by lymphoid tissue was so generalized that, in all probability, no adrenalin was secreted by these organs. We are still at a loss to account for the very extensive substitution of the adrenal medulla by lymphoid tissue. We are inclined to believe, however, that the replacement of the medulla by lymphoid tissue was responsible for the hypoglycemia and for the cause of death of the patient.

Discussion. If we accept as an established fact that marked hypoglycemia may in itself be fatal, it becomes very probable that the hypoglycemia is the principal cause of death, independent of whether it is due to hyperinsulinism resulting from a tumor of the islands of Langerhans, or due to an impaired function of the adrenals because of pathologic changes in these organs. The symptoms observed in our 2 patients were characteristic of hypoglycemia and showed the same general type and degree as those seen associated with fatal cases of hyperinsulinism. Everyone is familiar with the usual symptoms of hypoglycemia that occur in individuals receiving an overdose of insulin, as in the course of treatment in diabetes. All these symptoms were rather typically expressed in our 2 patients and suggested that we were dealing in each case with a similar pathologic process causing a disturbance in the normal balance of the blood sugar.

The various activities taking place in the body during the process of carbohydrate metabolism are very complex, for we have to deal

here not with a simple chemical change, but rather with a complicated mechanism which involves the activities of the various endocrine glands in the body. We are particularly concerned in this paper with the specific effects which the secretions derived from the cells of the islands of Langerhans and of the adrenals have on the metabolism of sugars. Pathologic changes in any of these glands of internal secretion may lead to a fatal hypoglycemia, although the mechanism of their respective actions in inducing such a condition is different in each case.

The hypoglycemia that is found in association with tumors of the islands of Langerhans can best be explained on the basis of increased as well as perverted insulin production. Our knowledge concerning the effects of insulin on sugar metabolism has gained rapid momentum ever since Banting and Best first discovered this substance. As a result of these various experiences we are able to diagnose quite accurately an attack of insulin shock, the symptomatology of which is here briefly recapitulated. It consists of sweating, nervousness, muscular twitchings, convulsions, coma and death. Such a symptom complex is also observed in individuals who have a tumor of the islands of Langerhans. This starts us therefore upon a line of thought which leads to a significant conclusion, namely, that a diagnosis of an island tumor could be very readily made in the presence of such symptoms as have been just described. The typical category of a hypoglycemic attack represents as a rule no unusual diagnostic difficulties, provided of course one keeps in mind the fact that the disease is far from being uncommon. Yet, it is very surprising to find only a very small percentage of these cases being accurately diagnosed, even by the most skillful and painstaking physician. The chief difficulty in making a correct diagnosis is usually due to the very close similarities existing between this disease and an allied number of neurologic disturbances. For this reason we find that many of these patients are referred to the neurologist for diagnosis. The symptoms which these patients present, however, are so unique that it is hardly conceivable they should be overlooked.

Reference has already been made to the exceedingly small size tumor of the pancreas which is held responsible for the hypoglycemia. The histologic studies made of these types of tumors justifies the assumption that they arise from the cells composing the islands of Langerhans. These tumor cells are found to have staining properties very similar to those known to occur in the normal beta cells of the insular portion of the pancreas. These cells are also apparently capable of elaborating insulin or an insulin-like substance, as judged from the body reaction in their presence. We feel, however, that the character of this secretion is somewhat different from the normal insulin, particularly insofar as it is much more potent. Such a conclusion is justifiable, we believe, if we consider the

extreme degree of hypoglycemia that may occur as a result of such an unusually small size tumor.

Of much interest to us is the part played by the adrenal glands in carbohydrate metabolism. This phase of the problem is intricate and still obscure. Clinical data as well as experimental findings point to the fact that one of the functions of adrenalin is to render sugar available for body use. The manner by which it brings this about is not definitely determined, although it is generally believed that it does so by setting sugar free from its normal depots in the liver. It appears then that in cases where this secretion is diminished or entirely lacking to the organism, the blood sugar is correspondingly reduced. It is also felt that the rôle which the adrenals play in the sugar economy of the body is of vital importance to the organism, so much so that complete absence of their secretion may lead to a fatal hypoglycemia. This phase of the problem is very well illustrated in our second case described above. We have noted in this patient all the clinical symptoms of hypoglycemia and the chemical changes were equally significant of a most marked reduction in blood sugar. Postmortem examination and cytologic studies made of the various organs of this patient revealed changes that were entirely confined to the adrenals, while all the other organs, particularly those concerned with carbohydrate metabolism, showed no evidence of any pathologic abnormality. In view of these findings we are justified in associating the hypoglycemia with the lesions in the adrenals. Similar observations were made by other investigators who reported all degrees of blood-sugar disturbances caused primarily by some adrenal disease.

The chief pathologic lesion in the adrenals of the case under discussion was located in the medulla, whereas all other parts of the glands escaped any appreciable damage. It will be remembered, however, that the adrenal medulla is primarily concerned with the formation of adrenalin, and that the latter is the sole product of these glands which influences the metabolism of sugar. It becomes evident, therefore, that in the absence of all medullary tissue no adrenalin will be formed to be available for body use. The resulting effects on carbohydrate metabolism then become quite obvious.

The pathologic changes described in the adrenals of our second case are very interesting. These changes, as will be remembered, consisted in total replacement of the medulla by dense collections of lymphocytes, many of which were arranged in groups around centrally placed reticuloendothelial cells, and gave the appearance of lymph follicle formation (see illustrations). These follicles were sharply demarcated from the surrounding stroma. They did not however, have a well defined germinal center as typically constructed lymph follicles are known to have. In the stroma between the various lymph follicles there was found scattered débris of preëxisting medullary tissue, together with numerous lymphocytes and

occasional giant cells. The exact significance of these lymphocytic collections is not very well understood and we cannot offer any plausible explanation for their widespread distribution in the adrenal medulla. A careful review of the literature has failed to reveal similar instances of hypoglycemia that arose primarily as a result of substitution of the adrenal medulla by lymphoid tissue. It may be theoretically assumed that the lymphoid changes in the adrenals represent a local manifestation of lymphoid dyscrasia, perhaps of some constitutional nature. Such assumptions, however, are conjectural and as such have not special merit. We therefore do not choose to interpret the pathogenesis of this peculiar case and simply content ourselves with reporting it. We are interested in the changes in the medulla at present only from the standpoint of their marked deleterious effects in bringing about a fatal hypoglycemia as described.

From the foregoing discussion it will be evident, we are sure, that several factors may come into play in causing blood-sugar disturbances. Of these the secretions derived from tumors of the islands of Langerhans and the sequelæ of depressed functional powers of the adrenals have been shown to account for some cases of hypoglycemia. A general analysis of the clinical symptoms and of the chemical changes in the blood in these two types of cases shows them to be identical. It therefore becomes a very puzzling problem when one seeks to establish the anatomic seat of the lesion in such patients. Very often it may be a life-saving matter to the patient if the anatomic lesion responsible for the hypoglycemia could be accurately established. As has already been shown, a curative result could be expected in cases where the hypoglycemia is caused by an accessible tumor in the pancreas. With the above facts in mind it is the authors' opinion that surgical intervention should be contemplated whenever a diagnosis of an insular tumor of the pancreas has been definitely made. It is quite obvious that such measures of treatment are entirely out of the question when the cause of the hypoglycemia is due to extensive involvement of the adrenals. Unfortunately, there is no specific test which may be employed in order to differentiate between these two lesions, for both a tumor of the island tissue of the pancreas as well as pathologic conditions of the adrenals may give rise to all degrees of blood-sugar disturbances. Both types of cases also respond equally well to glucose. It is possible, however, that in cases where the adrenals are at fault, other significant clinical and laboratory facts may be found which would shed more light and serve to establish a more definite relationship between the disease process in the adrenals and the accompanying hypoglycemia. In the light of such experiences it becomes obvious that we must always take into consideration all the various causes of the existing hypoglycemia before rendering an anatomic diagnosis.

Summary. 1. The various phases of hypoglycemia are discussed. Two cases of hypoglycemia are reported, one of which (previously published) was caused by a tumor of the islands of Langerhans, while the other was due to adrenal insufficiency.

2. The changes in the adrenals in the second case consisted in complete substitution of the medullary portion by lymphoid tissue. These changes were believed to account for the hypoglycemia in this patient.

BIBLIOGRAPHY.

1. Nadler, W. H., and Wolfer, J. A.: Arch. Int. Med., 1929, 44, 700.
2. Pettersson, A. S.: Acta med. Scand., 1928, 69, 232.
3. Anderson, H. B.: AM. J. MED. SCI., 1930, 180, 71.
4. Wilder, R. M., Allan, F. N., Power, M. H., and Robertson, E. H.: J. Am. Med. Assn., 1927, 89, 348.
5. Thalheimer, W., and Murphey, F. D.: J. Am. Med. Assn., 1928, 91, 89.
6. McClenahan, W. U., and Norris, G. W.: AM. J. MED. SCI., 1929, 177, 93.
7. Howland, G., Campbell, W. R., Maltby, E. J., and Robinson, W. L.: J. Am. Med. Assn., 1929, 93, 674.
8. Carr, A. D., Parker, R., Groves, E. W., Fisher, A. O., and Larimore, J. L.: J. Am. Med. Assn., 1931, 96, 1363.
9. Womack, N. A., Gnagi, W. B., and Graham, E. A.: J. Am. Med. Assn., 1931, 97, 831.
10. Smith, M. G., and Seibel, M. G.: Am. J. Path., 1931, 7, 723.

HUMAN PANCREATIC SECRETION STUDIED FROM A CASE OF PANCREATIC CYST WITH FISTULA.

By JOS. KAHN,

ISIDORE HERNSHEIM RESEARCH FELLOW IN CHEMISTRY,

AND

HERBERT M. KLEIN, M.D.,

MOSES HEINEMAN RESEARCH FELLOW,
NEW YORK CITY.

(From the Surgical Service of Dr. A. A. Berg and from the Laboratories of Mount Sinai Hospital.)

THE opportunity of studying the human pancreatic secretion as it is discharged directly from the pancreas, before it has entered the duodenum, is extremely rare. A survey of the literature reveals a scant knowledge of the enzymatic nature of the secretion. The following case afforded the opportunity to examine a relatively pure pancreatic fluid. The results of some of our investigations on the enzymatic nature of the external pancreatic secretion are presented.

Case Reports. CASE 1.—*History.* The patient, N. F., a native letter-carrier, aged 34 years, was admitted on April 5, 1930, to the Mount Sinai Hospital, on the surgical service of Dr. A. A. Berg. Eight years before he began to suffer from abdominal symptoms. At that time he was seized

with attacks of cramplike pains in the abdomen, not localized, and associated with vomiting. These seizures occurred as a rule a half hour after meals and were unrelieved by food. For $4\frac{1}{2}$ years, despite medicinal and dietary treatment, the pain and vomiting persisted. During this time his appendix was removed, without relief of his symptoms. Roentgenographic examination of the gastrointestinal tract revealed evidences of a diseased gall bladder. The patient was then put on a low fat diet, and was practically free from his symptoms for the next $3\frac{1}{2}$ years. Five months before admission he had a sudden attack of severe abdominal pain which lasted 1 week. At this time the gall bladder could not be visualized by the dye test. Three months later there was a recurrence of vomiting. This became progressively worse so that, in the week prior to his admission, every meal was followed by emesis. Pain was no longer present. Food particles in the vomitus represented material eaten at the preceding meal. There was no melena, no acholic stools, no jaundice. For the 5 months prior to admission there had been anorexia and marked constipation, with a loss of 35 pounds during this time.

A gastrointestinal examination with the aid of a barium meal was made by Dr. S. J. Goldfarb.* This showed that the normal acute angle at the junction of the first and second portions of the duodenum was changed to almost a semicircular form, indicating a separation of the first and second duodenal segments by an enlargement of the head of the pancreas. In view of the history of previous gall bladder disease, an acute attack of abdominal pain with subsequent vomiting and the Roentgen findings, a diagnosis was made of a pseudocyst of the head of the pancreas causing obstruction of the pylorus and duodenum by pressure.

Physical Examination. The patient was a moderately well-developed young man, showing evidences of considerable loss of weight. Physical examination of the internal organs was essentially negative except for the following findings: There was a large mass palpable in the right upper quadrant of the abdomen, non-tender and descending with respiration. It felt cystic and was approximately 3 inches in diameter. A succussion splash could be elicited in the left upper quadrant, presumably originating in the stomach. The stomach outline could not be definitely determined. The temperature was 99.8°F. , the pulse 110 and the respiratory rate 20.

The laboratory findings included: Hemoglobin, 104 per cent; white blood cells, 9200. Differential count: polymorphonuclears, 55 per cent; lymphocytes, 42 per cent; mononuclears, 3 per cent. The blood Wassermann test was negative. Blood analyses showed: Urea nitrogen, 21 mg. per 100 cc.; sugar, 95 mg. per 100 cc.; cholesterol, 180 mg. per 100 cc.; chlorid, 678 mg. per 100 cc.

The urine was clear, alkaline to litmus and had a specific gravity of 1.018; it showed a trace of albumin, no sugar, and only triple phosphates present in the sediment.

The stomach was aspirated, and 8 ounces of coffee-ground fluid obtained, giving a positive guaiac reaction for blood.

Laparotomy Findings. In view of the complete nature of the obstruction, operative relief was urgently indicated. Laparotomy was performed by Dr. A. A. Berg on April 12, 1930. On opening the peritoneal cavity, a large cystic mass could be felt in the retroperitoneal tissues in the upper portion of the abdomen just to the right of the midline, probably arising from the pancreas. Stones were felt in the gall bladder. Aspiration of the mass yielded 175 cc. of dark, slightly viscid liquid material. An approach was made through the inferior aspect of the transverse mesocolon and the cystic mass incised. There was found a cyst with a thickened

* Dr. S. J. Goldfarb will shortly report this case from the roentgenologic point of view.

and indurated wall, from which could be scraped a blackish material. The cavity of the cyst extended downward toward the pancreas and seemed to be intimately connected with it. A large rubber tube was placed in the cyst cavity and sutured by means of chromic catgut to the cyst wall. The parietal peritoneum of the left margin of the incision was then sutured to the wall of the cyst cavity by means of chromic sutures and the abdomen then closed in layers.

Course. In the week after operation the patient drained through the tube in the cyst 32 ounces of thick, brownish fluid. Several days later the patient began to drain large amounts of an opalescent, cloudy fluid, alkaline in reaction with a peculiar disagreeable odor. This was found to contain large amounts of pancreatic enzymes. As much of this fluid as could be swallowed was fed back to the patient. Despite its unpleasant odor, as much as 33 ounces of this material was taken daily by the patient. The fluid was collected under strictly hygienic precautions and did not prove distasteful to the patient. Drainage through the tube continued for 59 days after the operation. It gradually diminished in quantity and finally ceased entirely. The tube was then removed and the tract permitted to fill in by granulation tissue.

The postoperative blood chemical findings were always normal. There was no evidence of acidosis, alkalosis or disturbance in the carbohydrate metabolism except for one period, mentioned later on, when the patient was kept on a pure carbohydrate diet. Shortly after operation the patient began to develop a voracious appetite, so that he had to be fed almost hourly, with a daily intake of 5000 to 6000 calories. The diet was well-balanced. The stools were not fatty and contained only rare undigested meat fibers. Defecation occurred with customary frequency. There was no diarrhea. The patient felt well, gained weight rapidly and was discharged, asymptomatic, 67 days after the operation. Four months later he was perfectly well, had been free from symptoms on a low fat diet and had gained about 30 pounds. He felt normal in every respect.

In view of the opportunity offered of collecting presumably pure pancreatic juice, some investigations of the pancreatic secretion were undertaken. The material studied consisted of fluid drained through the tube inserted into the cyst cavity at operation and caught in a glass container. The secretion was kept on ice from the time collected until it was analyzed, generally on the next day. A Rehfuß tube was passed into the duodenum on two occasions after operation and both times pancreatic ferments were obtained, proving that some pancreatic secretion was entering the duodenum.

Pathologic Anatomy. The portion of the cyst wall removed at operation consisted of pancreatic tissue with areas of necrosis, chronic inflammation and fibrosis. The fluid aspirated from the cyst contained only débris; no cellular sediment was present.

Clinical Summary. Five months before admission the patient suffered from severe abdominal pain for 1 week. Thereafter vomiting, which had occurred rarely in the previous 3 years, became increasingly frequent up to the time of admission. The period of 1 week's pain probably represents the time when the patient was suffering from an attack of acute pancreatic fat necrosis with resulting destruction of pancreatic tissue and the formation of a pseudocyst, *i. e.*, one not resulting from the retention of secretion after blocking of a duct. This cyst grew steadily larger, causing progressive obstruction of the alimentary canal by external pressure on the pylorus and duodenum. By the operative drainage of the cyst the

pressure was relieved and the vomiting ceased. Postoperatively there was discharge of pancreatic secretion into the duodenum (pancreatic enzymes were found in the duodenum by duodenal bucket) and from the tube inserted into the cyst cavity. The

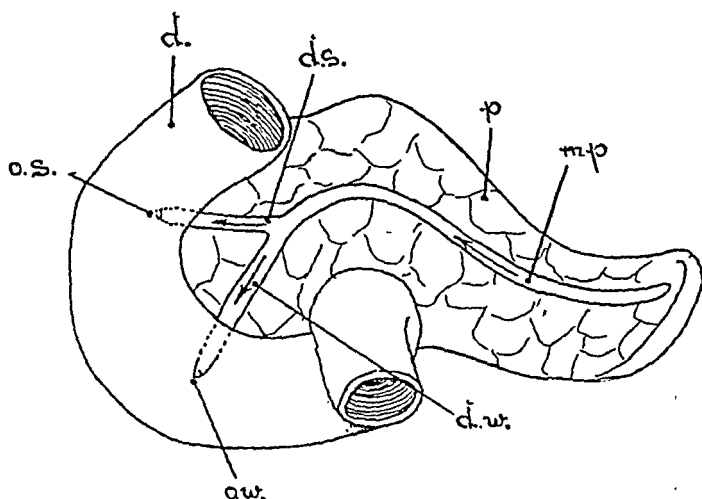


FIG. 1.—Schematic sketch showing a frequent relationship of the pancreatic ducts, modified after Schmieden and Sebening. *d.*, duodenum; *p.*, pancreas; *mp.*, main pancreatic duct; *dw.*, duct of Wirsung; *ds.*, duct of Santorini; *ow.*, opening of duct of Wirsung into duodenum (papilla Vateri); *os.*, opening of duct of Santorini into duodenum.

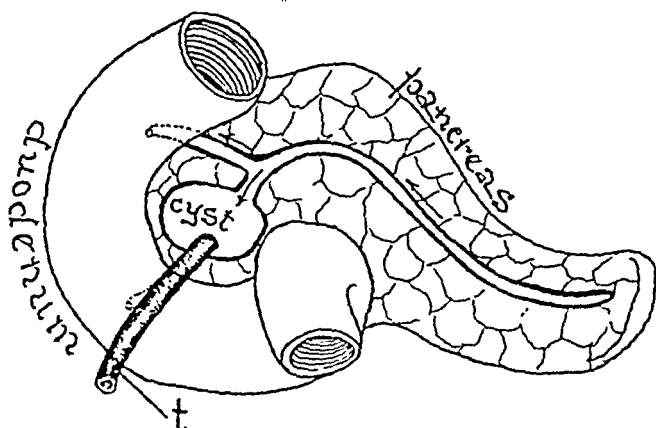


FIG. 2.—Status of flow of pancreatic secretion after operation, indicating presumed common communication of drainage tube and duct of Wirsung with cyst cavity. *t.*, drainage tube inserted into cyst cavity.

external drainage gradually decreased and finally ceased 59 days after operation. Opie (1903), Schmieder and Schering (1927) and others have demonstrated that there is frequently an anastomosis between the ducts of Santorini, Wirsung and that draining the

main portion of the pancreas. This relationship is schematically presented in Fig. 1. Fig. 2 represents our conception of the pathologic changes present in our case, indicating the communication between the cyst cavity and one of the outlet ducts of the pancreas. Because of the presence of pancreatic ferments in the duodenum, it is presumed that there was another outlet duct discharging into the duodenum and not into the cyst. In view of the large amount of the fistula drainage, it is probable that the major duct (Wirsung) communicated with the cyst. It is our view that as healing progressed there was gradual obliteration of the cyst cavity with consequent closure of the communication between cyst and duct. The other duct (Santorini) probably assumed the rôle of draining that portion of the pancreas previously drained by the duct of

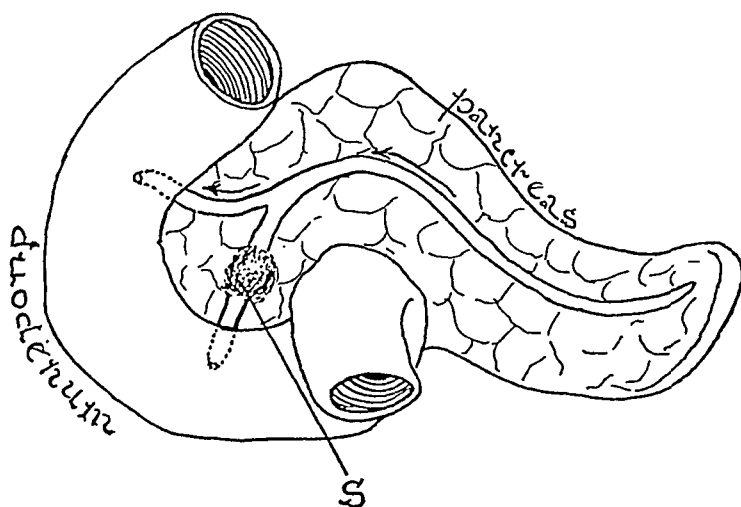


FIG. 3.—Status of flow of pancreatic secretion after cessation of drainage through tube. *s*, scar at seat of obliterated cyst cavity. NOTE.—Communication between cyst and duct of Wirsung no longer exists; entire pancreatic secretion entering duodenum *via* the duct of Santorini.

Wirsung so that finally all the external secretion of the pancreas was entering the duodenum through the duct of Santorini. (Fig. 3.)

Pancreatic Juice Findings. The pancreatic juice studied was opalescent and had a peculiar distasteful odor, somewhat resembling that of decomposing meat. The pH was 8.2. The specific gravity was 1.005. The total solid content varied from 2 to 3 per cent, of which 1 per cent consisted of organic substances.

Appetite Secretion. Although there was a continuous discharge of secretion from the tube, a great acceleration in the rate of discharge occurred after the ingestion of food. Between the time of ingestion of food and the noticeable increase in the rate of secretion there was an interval varying from 20 to 50 minutes. No relation was observed between the type of food eaten (*e. g.*, carbohydrate, protein, fat) and the duration of this interval. In order for the

acceleration of secretion to occur food had to be swallowed. Efforts to induce a "psychic secretion" were unsuccessful. The interval was interpreted as representing the amount of time elapsing before the food swallowed entered the duodenum, and there, by the action of the acid chyme on the duodenal mucosa, excited the pancreatic secretion (secretin formation).

Amount and Enzymatic Potency of the Secretion. We have set down in Table 1 the amount and the enzymatic potency of the fistula secretion collected from May 25 to June 9. During this time the patient was eating a well-balanced diet averaging 5000 to 6000 calories daily.

TABLE 1.—ENZYMATIC CONTENT OF FLUID FROM PANCREATIC FISTULA.

Date.	Drainage, cc.	Lipase units, cc.	Trypsin units, cc.	Diastase units, cc.	Total lipase secretion, units.	Total trypsin secretion, units.	Total diastase secretion, units.
May 25	1360	2.2	0.13	0.067	3000	410	9.1
26	1060	3.2	0.60	0.061	3400	640	6.5
27	1120	3.0	0.50	0.066	3350	560	7.4
28	770	3.2	0.75	0.090	2450	580	6.9
29	1390						
30	790	7.0	1.20	0.127	600	160	10.8
31	1300	1.3	0.50	0.070	1700	650	100.0
June 1	1180	2.0	1.50	0.040	2350	1780	47.5
2	890	2.3	2250		
3	920	2.15	1950		
4	130						
5	210	3.5	750		
6	620						
7	800	7.5	6000		
8	740						
9	410	5.5	2300		

As enzymes have not been isolated in pure form, their quantitative estimation cannot be based on absolute amounts by weight, but must be arbitrarily expressed by a definition which refers to their digestive potencies. Such definitions have been given by Willstätter (1923 etc.) and his coworkers in their experimental work aiming at the purification and concentration of ferments from the pancreas and other glands. We thought it advisable to adopt their standards for the titration of the enzymatic activity of the fistula juice. This permitted ready comparison between the amount of digestive enzymes excreted through the fistula and the amount usually encountered in the gland itself.

The detailed reasons for the choice of the following "unit" definitions are to be found in the work cited above. They were chosen by Willstätter and his associates because they represent the average amount of the individual enzymes contained in 10 mg. of dried hog pancreas.

One lipase unit is the amount of lipolytic enzyme that hydrolyzes 0.6 gm. of olive oil when incubated with 2.5 gm. of olive oil at 30° C. for 1 hour in the presence of the necessary activators.

One trypsin unit is the amount of proteolytic enzyme that liberates 3 mg. of amino-N from 300 mg. of casein dissolved in 10 cc. of water at a pH of 8.9 when they are incubated for 20 minutes at 30° C. This represents about one-tenth of the amino-N of the casein susceptible of enzymatic digestion.

The definition of one amylase unit involves the calculation of the reaction constant. It amounts to approximately 100 times the amount of the enzyme that will split 25 per cent of 0.25 gm. of starch when it is incubated for 17.5 minutes at 30° C. and at pH 6.8.

For instance, 1 cc. of the pancreatic juice collected May 25 contained 2.2 lipase units, 0.13 cc. trypsin units and 0.067 amylase units. This means that within 1 hour and under optimal conditions 1 cc. would effect a 24 per cent saponification of $2.2 \times 2.5 = 5.5$ gm. of olive oil, would liberate one-tenth of the amino-N of 127 mg. of casein ($300 \times 0.13 \times \frac{6.0}{2.0}$) and in the same time would convert into sugar one-fourth of 8 gm. of starch.

It is impossible at the present time to draw a comparison of the enzymatic content between human fistula juice and human pancreas gland, since no data have been published for the latter. Deutsch and Grubel (1927) made a quantitative study of a human pancreatic cyst fluid. They found 0.0067 amylase unit per cc., which is one-tenth of the average for the present fistula fluid. Their determination of lipolytic enzyme is based on the hydrolysis of tributyrin and cannot be compared to lipase action as measured by triolein cleavage. They found that the trypsin in the cyst fluid was not in an activated state; however, they did not determine the actual trypsin content after addition of the activator enterokinase. The results of previous studies of pancreatic cyst fluids, quoted by Deutsch and Grubel, do not permit a quantitative evaluation of the enzymes.

Studies of the fistula juice from animals have been confined to dogs. Waldschmidt-Leitz and Waldschmidt-Graser (1927) compared fistula juice from dogs with the dry glands of dogs and hogs. The enzymatic content of 1 cc. of juice approximated the content of 0.05 to 0.1 gm. of dry dog pancreas for the enzymes investigated. Hog pancreas was found much richer in enzymes, especially in lipase.

If we assume that the enzymatic content of human pancreas is of the same magnitude as that of hog pancreas, then 25 gm., the average weight of a dried human pancreas, should contain about 2000 to 3000 lipase units, 2000 to 3000 trypsin units and 1000 to 1500 amylase units. The amounts discharged daily from the fistula in the present case varied from 600 to 6000 units of lipase, from 160 to 1800 units of trypsin and from 6 to 100 units of amylase.

From these observations three conclusions can be drawn: (1) There was no constancy in the ratio of lipase : trypsin : amylase on various days and no necessary relationship among the amounts of the individual enzymes secreted. Variations in the dietary constitution might have thrown some light on this question and on the question of specificity of secretin. Experiments along these lines could not be carried out, because the patient went into collapse for some reason which could not be determined when placed for a few days on an almost pure carbohydrate diet. Farrell and Ivy (1926) did not find any qualitative difference in the enzymatic content of the pancreatic excretion when dogs with pancreatic fistulas were put on extreme fat, carbohydrate or protein diets. (2) A comparison between the proportion of the various enzymes present in the fistula juice and their proportion in normal dried hog pancreas shows a relative increase in the amount of lipase in the former. This may have been due to the fact that the pancreas is practically the sole source of the body lipase. In disease of pancreas the protein- and starch-splitting enzymes may possibly be supplied by other secretions of the body (pepsin, erepsin and ptyalin, etc.). (3) There was a different rate for the secretion of the various enzymes and therefore a different rate for the discharge of the total amounts of the individual enzymes, theoretically present in the pancreas at one time, with corresponding variation in the frequency of renewal of the supply of enzymes in the gland.

There was no digestion of the tissues of the abdominal wall, despite leakage along the drainage tube. In view of the fact that such digestion does occur in some cases of pancreatic fistula, *e. g.*, that described by Fast (1930), a portion of the fistula secretion was analyzed immediately after discharge in order to throw some light, if possible, on the mechanism of digestion of the tissues of the abdominal wall.

The following experiment was performed: (1) 1 cc. of the fistula juice of May 5 was allowed to act on 300 mg. of casein for 1 hour. An increase in the acidity of the solution was not observed. (2) 1 cc. of the same secretion after activation with the amount of enterokinase obtained from $\frac{2}{3}$ gram of human duodenal mucosa for 30 minutes when allowed to act on casein for 20 minutes caused the liberation of an amount of acid neutralized by 0.3 cc. of $\frac{N}{6}$ KOH. The enterokinase was prepared from human duodenum, according to the directions of Waldschmidt-Leitz. (3) The enterokinase extract alone produced no increase in the acidity when allowed to act on casein.

In the light of these results it appears that digestion of the tissues of the abdominal wall around the wound does not occur if the trypsin in the secretion discharged is not activated. Similar experiments would be desirable in cases where tissue digestion does occur. In the case of Fast there was probably admixed a sufficient amount

of tissue juice, from the abdominal area drained, to activate the trypsin.

Summary. A case of pancreatic cyst was studied which, after operation and prolonged drainage through a fistula led to complete recovery. The course of the disease and the healing process are interpreted and the probable site of the cyst relative to the pancreatic ducts is discussed.

In a study of the enzymatic output no constancy was found in the ratio lipase:trypsin:amylase secreted. The daily output of these enzymes, when compared with their amounts estimated to be present in the gland, was found to represent a large proportion of the lipase present and a much smaller amount of the amylase and trypsin. The latter was found to be free of enterokinase. This accounts for the fact that digestion of the tissue around the wound did not occur.

REFERENCES.

- Deutsch, W., and Grubel, H.: *Klin. Wehnschr.*, 1927, 6, 2369.
 Farrell, J. I., and Ivy, A. C.: *Am. J. Physiol.*, 1926, 78, 325.
 Fast, F. W.: *J. Am. Med. Assn.*, 1930, 95, 1668.
 Opie, E. L.: *Am. Med.*, 1903, 5, 996.
 Schmieden, V., and Sebening, W.: *Arch. klin. Chir.*, 1927, 148, 319.
 Simkins, Samuel: *AM. J. MED. SCI.*, 1931, 172, 626.
 Waldschmidt-Leitz, E., and Waldschmidt-Graser, J.: *Ztschr. f. physiol. Chem.*, 1927, 166, 247.
 Willstätter, R., Waldschmidt-Leitz, E., and co-workers: *Ztschr. f. physiol. Chem.*, 1923, 125, 93; 126, 143; 1923-24, 132, 181; 1926, 161, 191. See also Oppenheimer, C.: *Die Fermente*, Leipzig, 1925.

FURTHER OBSERVATIONS ON THE USE OF DEXTROSE IN PNEUMONIA.

BY W. W. G. MACLACHLAN, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE,

GEORGE J. KASTLIN, M.D.,

INSTRUCTOR IN MEDICINE,

AND

RALPH LYNCH, M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

(From the Medical Clinic, Mercy Hospital, Pittsburgh, and the Department of Medicine, University of Pittsburgh.)

In a previous report¹ on the subject of dextrose therapy in pneumonia, we stated that the value of this treatment must be gauged by the results obtained in the cases that had positive blood cultures. And when we concluded, in this earlier study, that dextrose was of value as a supportative measure, we did so largely because the mortality, in our positive blood culture cases, had improved while this treatment was being used; the mortality in the positive culture

cases of our second series (1928, 1929) was 22 per cent better than it had been in the first series (1925-1928). We were impressed with this improvement, and our tendency was to attribute it to the use of dextrose.

We have continued this study, and the present report includes the observations made during the period 1929 to 1931. Postoperative collapse of lung, postoperative pneumonia and the pneumonia of children are not considered in this report.

Methods. Dextrose was given by mouth in the form of lemonade, 150 to 200 gm. to each quart, and between 1 and 2 quarts were taken each day. This dextrose drink was given routinely to all cases of pneumonia. There appeared to be a considerable variation in the ability of patients to drink lemonade, as some were able to take it freely throughout the disease, while others became nauseated in a day or two, and the further giving of dextrose by this method became impossible. In the cases that showed any degree of toxicity, dextrose was given by vein in a 25 per cent solution made up in normal salt solution. During the past year a continuous method of giving the intravenous injection was developed. As the apparatus is a simple and efficient one for intravenous therapy, a more detailed description of it will be given in another place.

The dextrose solution was given continuously over periods from 6 to 12 hours during the day, and as a rule from 1000 to 1500 cc. was received by the patient. It was continued in this way during the course of the disease. Thrombosis of the veins of the arm, unfortunately, was frequently noted after this continuous method.

An effort was made to give the greatest amount of dextrose that could be burned. In most cases, this maximum approximated between 50 and 60 gm. of dextrose per hour. Utilization of dextrose usually became unsuccessful, if the rate of intake of solution exceeded 200 cc. per hour. When dextrose appeared in the urine, it was usually because the solution had been given too rapidly. However, it is probable that, in some of the more toxic cases, the ability to burn sugar was decreased. The amounts of dextrose taken, and the timing of the inflow of solutions, were rather closely watched, and we are satisfied that dextrose was given adequately, to the great majority of the cases.

TABLE 1.—GENERAL MORTALITY AND BLOOD CULTURE DATA.

	Cases.	Mortality, per cent.	Blood cultures taken, cases.	Blood cultures, positive.	
				No. cases.	Per cent.
1925 to 1928 . .	160	43	72	19	26.3
1928 to 1929 . .	126	42	97	29	29.7
1929 to 1931 . .	249	45	218	100	47.7
	535		387		

Results.—The above table shows that the general mortality has been about the same over a period of 6 years. The number of cases in which blood cultures were taken has increased, and the actual number of cultures in the last 2 years is more than double the number of cases. We would call attention to the increasing percentage of positive blood cultures. In the last 2 years, this increase has been chiefly due to repeating the cultures on cases which were at first negative.

The following table indicates the mortality in the positive and negative blood culture cases.

TABLE 2.—POSITIVE BLOOD CULTURES.

	Cases.	Deaths.	
		No.	Per cent.
1925 to 1928	19	14	73.7
1928 to 1929	29	15	51.0
1929 to 1931	100	74	74.0

NEGATIVE BLOOD CULTURES.

	Cases.	Deaths.	
		No.	Per cent.
1925 to 1928	53	16	30.2
1928 to 1929	68	22	32.0
1929 to 1931	118	15	12.7

During the years 1928, 1929 in the positive group a considerably better mortality was noted over the previous years; but the actual number of cases was small. At this time, we were not estimating the pneumococcus count, and from what we now believe, it is very probable that our better results in this year were due to the fact that many of the positive cases represented those with very low counts per cubic centimeter of blood. The very high mortality in a much larger series during the past 2 years is in keeping with the figure generally quoted for positive blood culture cases (not serum-treated). The negative blood culture group shows a marked decrease in mortality in the last 2 years. The relatively low mortality in the negative blood culture group in the past 2 years is in striking contrast to the positive group. Practically five-sixths of the fatal cases showed positive blood cultures.

Comment. During the past 2 years we have carried out the blood culture studies on a much greater scale. This was done, first to establish more definitely the incidence of pneumococci in the blood in our fatal cases, and second to be able more easily and accurately to estimate the value of the dextrose therapy. Blood cultures were not repeated if found positive, but if negative, while the clinical course of the patient still indicated a toxic state, they were repeated a number of times. The fatal cases that had negative blood cultures during the greater duration of the disease, would nearly always have a positive culture at or near the end of the infection. Very few cases die with negative blood cultures, if the routine of repeating the cultures is closely followed. In our previous report we called attention to our very high negative blood culture mortality and stated that a more careful repetition of taking blood cultures would likely produce different results. Our present tables very clearly confirm this opinion. During the past year, blood agar plates have been made routinely at the taking of the blood culture so that the number of pneumococcus colonies could be estimated. We believe this procedure is an important one, particularly in reference

to prognosis. The plate, of course, often misses a growth that is observed in the broth. We have not encountered a case which has recovered (nonserum cases) with more than 15 colonies of pneumococci in 1 cc. of blood, and we have seen only 1 case with 15 colonies recover. In their early monograph on pneumonia, Avery, Chickering, Cole and Dochez² have spoken of these phases of blood culture work and it is interesting that in their group of nonserum treated cases with pneumococcus in the blood stream there were no recoveries where more than 15 colonies were found. The positive blood culture cases that recover must be those in which the colonies are very few; at least, this has been our experience. Fatal cases, however, may occur where only a few pneumococci are present. Further observations pertaining to this particular phase of blood culture work should be of considerable value and Koch³ has informed us of an interesting study, now in press, correlating the blood culture findings and prognosis. The positive blood culture group is an important one, because the severity of the disease in any community bears a close relationship to the number that have a bacteremia. As Topley⁴ remarks, the positive blood culture is an index of the severity rather than an accurate index of the presence of the organisms in the blood. Further, one is well able to agree with his statement that "the prognostic significance of a positive blood culture is one of the best attested facts which have emerged from the bacteriologic study of this disease." Any therapeutic measure that is to be considered in pneumonia must lower the mortality in this group of cases.

Dextrose has been given in adequate dosage during the past 2 years, and from the mortality figures in Table 2 there can be no other conclusion reached than that this method of therapy has failed. While we have seen symptomatic improvement frequently following the use of intravenous dextrose, and in some instances an almost dramatically favorable response, yet we are forced to admit that these good results were never seen in the positive blood culture cases where the pneumococcus count has been above 15 colonies per cubic centimeter of blood.

If we are to influence our mortality by treatment, this toxic or positive blood culture group must be affected. It is our opinion at the present time that supportative, or if we may say physiologic, methods are quite unable to accomplish this result. One wonders whether a similar series of positive blood culture cases, treated adequately in an oxygen tent, would show mortality figures any lower than those given in our tables for dextrose therapy. Osler's⁵ statement made in 1888 is still true: "there is no acute disease with so few cases in which the issue of life and death lies in the administration of drugs." It appears to us at the present time, more forcefully than ever, that the only hope in treating this disease in its toxic forms, is by directly counteracting the pneumococcic infection, or, in other words, specific therapy.

Conclusion. After a fair trial in the use of dextrose in the treatment of pneumonia, we have observed that it has not reduced the mortality and have, therefore, concluded that it has no essential place in the treatment of this infection.

BIBLIOGRAPHY.

1. MacLachlan, W. W. G., Kastlin, G. J., and Lynch, Ralph: *AM. J. MED. SCI.*, 1930, 179, 93.
2. Avery, O. T., Chickering, H. T., Cole, Rufus, and Dochez, A. R.: *Acute Lobar Pneumonia*, Monograph of the Rockefeller Institute for Medical Research, 1917, No. 7, 37.
3. Koch, K. R.: (Personal communication, article in press).
4. Topley, W. W. C., and Wilson, G. S.: *Principles of Bacteriology and Immunology*, 1929, 2, 1097.
5. Osler, William: *Univ. of Pa. Med. Mag.*, 1888-1889, 1, 77.

A CLINICAL STUDY OF ARTIFICIAL HYPERTHERMIA INDUCED BY HIGH FREQUENCY CURRENTS.

BY FRANCIS W. BISHOP,
ASSOCIATE IN MEDICINE (RADIOLOGY),

CHARLES B. HORTON, M.D.,
INSTRUCTOR IN MEDICINE (PSYCHIATRY),

AND

STAFFORD L. WARREN, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE (RADIOLOGY),

WITH THE TECHNICAL ASSISTANCE OF MISS EMMY LEHMAN, R.N.,
ROCHESTER, N. Y.

(From the Divisions of Radiology and Psychiatry of the Department of Medicine of the University of Rochester, School of Medicine and Dentistry, and the Strong Memorial Hospital.)

THERE are several methods of producing fever artificially in the human body. Some of these act indirectly while others act directly. The passage of high frequency currents through the body is a direct and rather quantitative procedure which can be controlled more carefully than any other method. The elevation of the temperature can be determined and accurately maintained by a simple and safe method which will be described. The use of this method in uncomplicated cases or cases not already impaired to the point of their being a poor surgical risk is practically devoid of danger. Other workers (King and Cocke³, Neymann,⁴ Hinsie and Carpenter²) have attempted to parallel, by this electrical method, the fever alternations of malaria therapy already used with considerable success in the treatment of paresis. We have felt that it was the

sum total of the fever bouts, rather than the short fever with intervals between, which was responsible for the clinical improvement of the paretics. This idea has its corollary in the occasional report of the subsidence of a chronic disease following an acute infection, usually respiratory, with a high temperature over a considerable period of time. Certain German workers in analyzing the results after malaria have added up the number of hours of fever above various temperature levels and have pointed out that the higher the temperature the shorter the period of fever necessary to bring about clinical improvement. Even at a temperature of 41°C . this total added up to quite a long time, somewhere around 48 hours, and at 40°C . 72 hours.

After careful survey of the clinical records of patients having high fevers, and after 2 years' preliminary work on dogs,¹ we set the limit of the therapeutic fever at 42°C . for the patient. Cases have been observed in which patients have survived higher temperatures than this, *i.e.*, insolation and sepsis. We know from our experience with 100 treatments that 42°C . is a dangerous temperature level, for more than a very short period. We can maintain temperatures slightly below this however (41.5° to 41.7°C .) for a period of at least 5 hours without difficulty or damage to the patient, and this has become our standard procedure. There are several reasons which dictate the choice of the 5-hour fever period in the treatment of disease by this method. It is the longest period well tolerated by the patient. It fits in well with the 8-hour working day for the personnel. It corresponds to preliminary studies of the thermal death time of certain cultures, especially gonococci, in water-bath experiments to be reported later, and most important of all it is long enough to be followed by clinical improvement.

At first we had great difficulty in obtaining enough power to raise the patient's temperature rapidly enough to make it possible to treat him in 1 day. The matter of heat insulation and the proper handling of the patient at all times during the procedure was another serious problem. After a great many changes the following method has now become practically standardized for the use of the "300-meter wave length" currents in this clinic.

Method. In order to eliminate the use of blankets, which are cumbersome and give the patient a sense of restraint, a cellotex chamber was built, which covers the patient and prevents loss of heat (Figs. 1 and 2). The upper portion is shaped like half an octagon. The lower half consists of a box containing a mattress, into which the upper half fits snugly, to prevent the leakage of heat. At one end a semicircle is cut to allow the patient's head to remain outside of this chamber (Fig. 2). There are 5 carbon filament lamps in the foot end of the box and 3 in the head end. These are controlled from the outside and maintain the air temperature within the box at a level sufficiently high to compensate for loss of heat by the patient through radiation, etc. (usually around 45°C .). Drapes surround the patient's neck to prevent leakage of air in this direction.



FIG. 1.—This shows the general arrangement of the cabinet and treatment machine and the various openings in the upper portion of the chamber which surrounds the body of the patient. The block-tin electrodes and the many-tailed surgical binder are visible on the top of the cabinet.

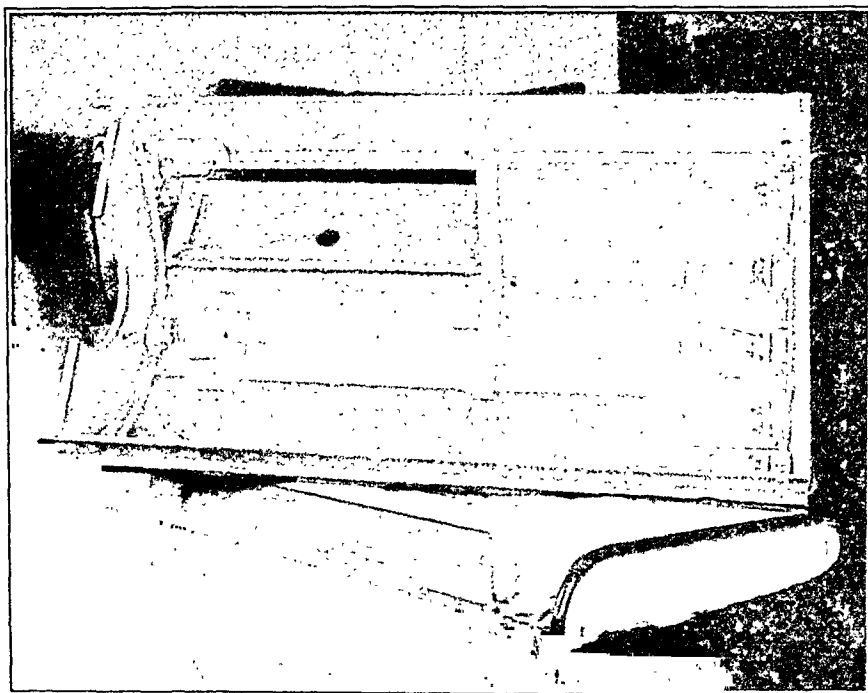


FIG. 2.—Detail of the interior of the half octagon cellotex cabinet showing the arrangement of the lights and the hole for the patient's neck.

Various apertures for the recording rectal resistance thermometer and electrocardiograph leads, etc., are present.

The patient is placed on the mattress and block tin electrodes, 28 by 46 to 60 cm., are bound on the anterior and posterior surfaces of the trunk by means of a many-tailed surgical binder. The patient is then covered by a sheet. The electrodes are connected to the high frequency machine. The lights within the cabinet are turned on and the rectal thermometer inserted. The pulse and respiration, as well as the temperature, are recorded every 10 minutes.

The high frequency apparatus is a slightly modified "diathermy" machine able to pass 5000 to 6000 milliamperes through the patient's trunk between the block tin electrodes.

Clinical Progress. After the current has been turned on it is raised as rapidly as the patient permits to between 5000 and 6000 milliamperes. No lubricant appears necessary, since the patient begins to perspire almost immediately. During the first 10 to 30 minutes no change may occur except for the rapid outpouring of perspiration. Then there is a flushing of the skin which may progress to the point where the patient becomes a deep red color (not cyanosis). Perspiration fairly runs off the skin. Immediately after this the temperature begins to rise and continues to rise at an even rate until the current is turned off. If the elevation of temperature has been rapid the rectal temperature may continue upward about a half a degree after the current is turned off, but if the rise has been fairly slow this continued rise will be reduced or may not occur. This is apparently due to the redistribution of the heat which has been absorbed by the trunk in the neighborhood of the electrodes. During the elevation of the temperature the rectal temperature is at first higher than the mouth temperature. When the body temperature reaches about 38° to 39° C. the mouth temperature usually becomes higher than the rectal temperature and remains so or equals it until the current is turned off. This, we believe, is due to the heating up of the lung substance faster than the blood can remove the stored heat, so that the expired air is hotter than the blood in the rectal vessels. As soon as the current is turned off the mouth temperature equals or becomes slightly less than the rectal temperature (Fig. 3).

When the required temperature level has been reached and the current turned off, the electrodes are removed from the trunk and the patient remains in the box covered only by a sheet. The air surrounding the patient is kept at an adequate level, and in so doing the patient's body temperature is maintained at the predetermined height. If, for any reason, the body temperature rises the surrounding air is cooled off. If it drops the air temperature may be raised as high as it can be tolerated (perhaps 50° C.) and slowly the body temperature is built up to the desired level.

Many patients become slightly delirious even though mentally normal beforehand. They are hypersusceptible to slight noises

and are apt to become excited and pugnacious. They sometimes lose all mental restraints and barriers, and their speech reverts to their fundamental type. With this excitement the pulse and respiration mount rapidly. If they are not quieted heat is produced by physical exertion in sufficient quantity to raise the body temperature still further (Fig. 4). Immediate measures must be taken to quiet the patient for the temperature is already near the upper safe limit. Often calmness and reassurance on the part of the

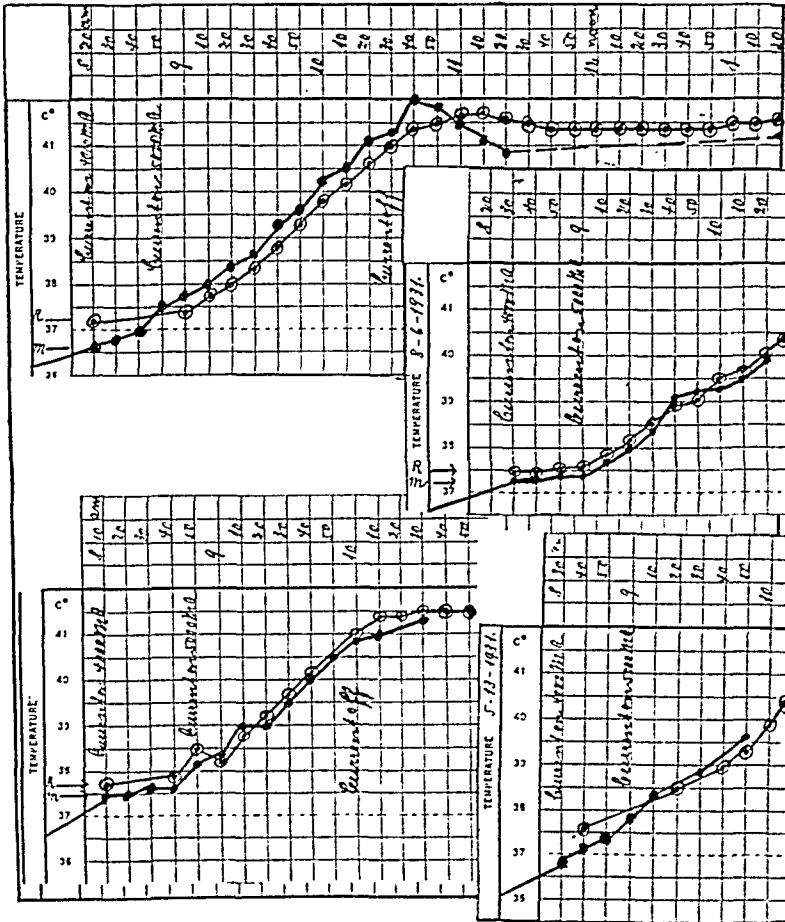
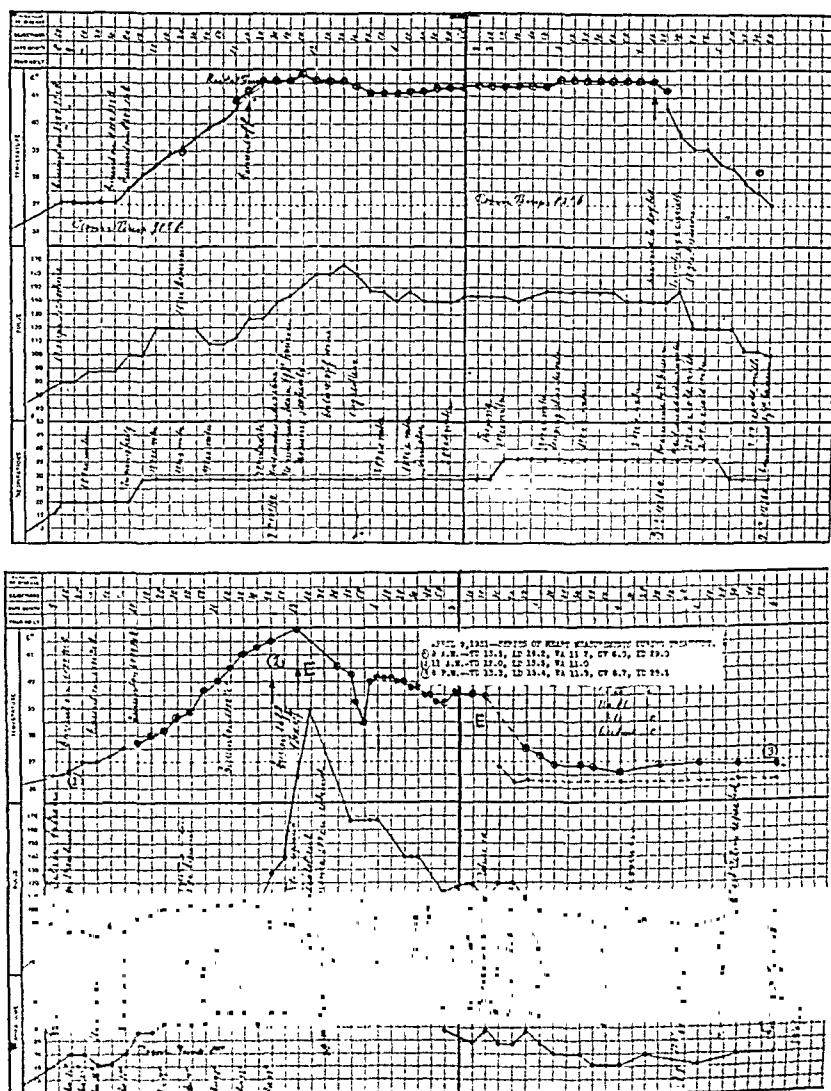


FIG. 3.—This chart shows the vagaries of the mouth (dots) and rectal (circles) temperatures during the establishment of the fever.

attending doctor and nurse, stroking of the patient's head, requesting him to be quiet while the blood pressure is taken and similar maneuvers are sufficient to quiet the patient. Many sedatives have been tried, but none well suited for general use has been found. All have some more or less serious disadvantage, the chief of which is the period of excitement produced by the drug before the narcotic stage is reached. Nearly all are depressants of the respiration or blood pressure or both. This is in keeping with

clinical experience with patients in delirium during high fever. Chloral hydrate in doses up to the narcosis point has been very



The pulse and respiration usually rise in keeping with the temperature (Fig. 3, *ff*). The pulse usually reaches a level between 130 and 150, where it may be maintained for the duration of the treatment. Periods of excitement are always indicated on the chart by a rise in the pulse rate. In nervous patients the entrance of the doctor or visitor can almost be registered by changes in the pulse of from 10 to 20 beats. During excitement the respiration may vary greatly as will be evident in some of the charts shown (Figs. 4 and 5). During the treatment the patient is allowed to drink as much warm fluid as he requests and is also given food if he wishes it.

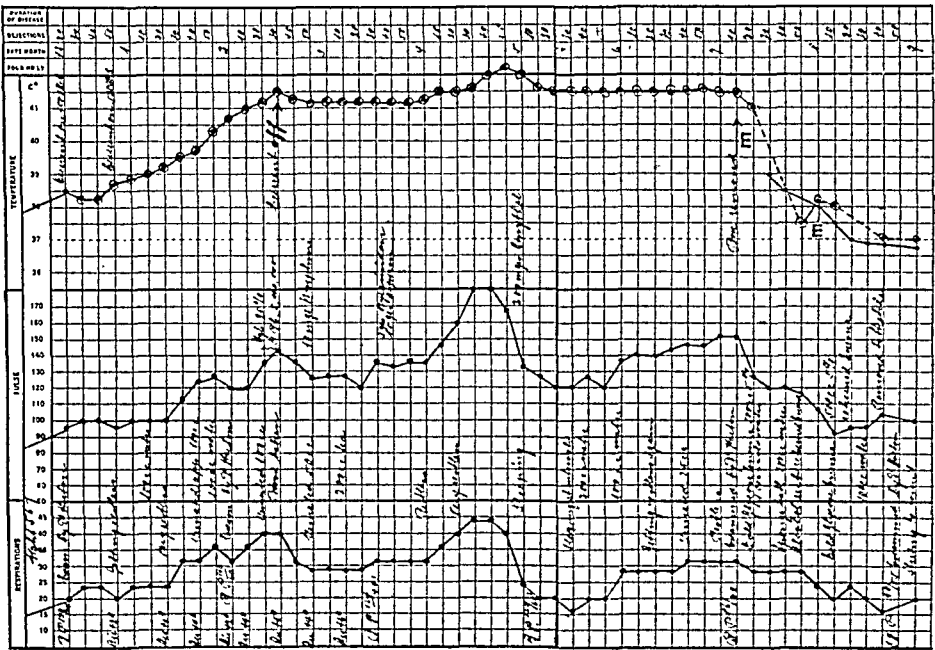


FIG. 5.—This chart shows the simultaneous variation in temperature, pulse and respiration as a result of restlessness. The effect of sedatives, cooling measures, and the subsequent continuation of the treatment as the patient quieted down are well illustrated.

When it is desired to terminate the fever the box is removed from over the patient and the body exposed to room air. It is possible to allow currents of very cool air to blow across the patient without causing a subsequent ill-effect. A drop in temperature of about 4° C. of the skin surface is apt to cause local shivering and contraction of the hair follicle muscles. If this occurs the patient is uncomfortable, and it is better to cover the body with a sheet. If nothing further is done the body temperature will gradually return to normal in about 3 hours. This may be expedited somewhat by alcohol and ice rubs, but these are not very efficient since the skin capillaries contract at the touch of the cold, and heat is

retained rather than radiated. It was found that a cold retention enema would greatly hasten the cooling process (Fig. 6). After

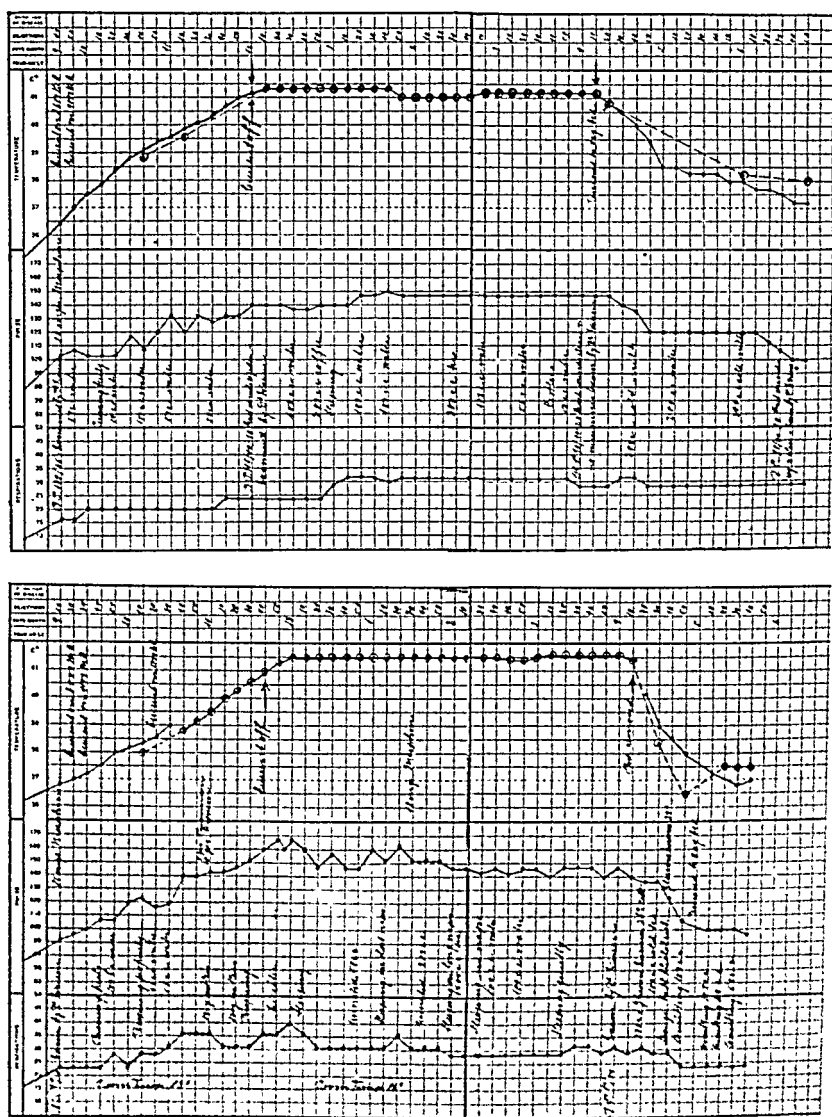


FIG. 6.—Temperature, pulse and respiration curves in a 50-year-old patient with chronic arthritis. Circles represent the rectal, and dots the mouth temperature. The lower chart illustrates a second treatment one month later and shows the effect of a cooling enema as compared to the upper curve where none was given. At this stage of development of the technique, treatments were restricted to 4 hours in cases of arthritis. Pulse and respiration curves show the normal variations.

removing the box 500 cc. of 0.6 per cent saline containing 25 gm. of glucose are instilled per rectum. The temperature of this fluid

may be as low as 10° to 15° C. without causing shock. Abdominal cramps are practically always present, but they are not severe. After 20 minutes or more another 500 cc. are given per rectum. By this procedure the temperature returns to normal within $1\frac{1}{2}$ hours after the removal of the box.

The patient should never leave the treatment room until the temperature has returned to normal. It is necessary to record the temperature only at hourly intervals thereafter for 4 hours. We have found in a few cases sent back with temperatures higher than normal that the temperature rose subsequently, but removing the covers was sufficient to bring it down again. In no patient who was returned with a normal temperature has there been a rise at a later period. We have not found the mouth temperature to go below 36.5° C.

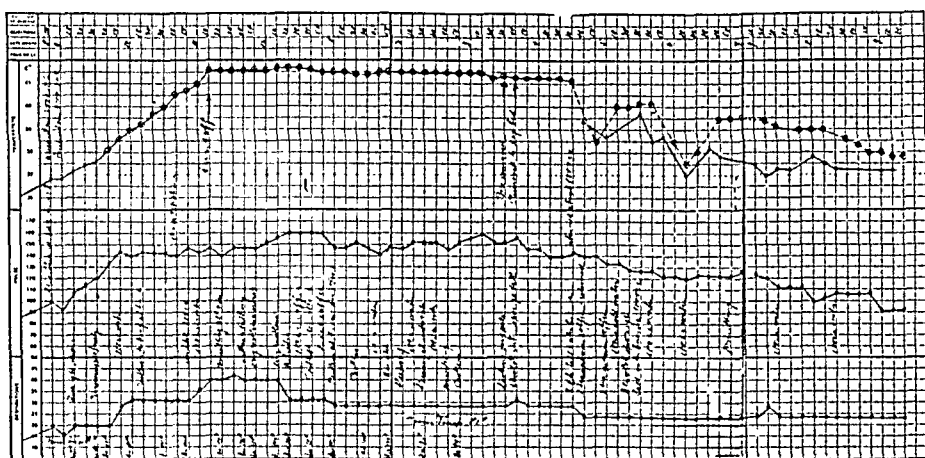


FIG. 7.—This was an obese 57-year-old arthritic patient who responded in the usual way to the fever treatment except for the delay in the fall of the temperature upon exposure to room air. Two cold enemas lowered the level of the temperature, but two hours longer than usual were required to bring the temperature back to its normal level. Further enemas were contraindicated because of vomiting and dropping blood pressure. Note the influence of the cold enema on the mouth temperature.

Immediately after removing the patient from the box the pulse and respiration begin to return to their normal, though occasionally both may remain slightly above their original levels for some time. The patients are given cold fluid to drink after removal from the box, though this is restricted to about 1000 cc., especially if a large amount was taken in during the treatment period. Too large an intake is apt to result in vomiting when the patient moves about or when he is shifted back to his own bed. Cold ginger ale, probably because of its sugar and alkaline content, is very well tolerated during this last period. Too much fluid intake may produce acute syncope in the period just after the enema is given, and in 1 patient who developed this symptom it was possible to demonstrate that the fluid content of the blood was greatly increased.

It occasionally happens in obese people that the temperature does not come down as rapidly as it should (Fig. 7), possibly due to insulation by the layers of fat. Colder enemas should thus be given to obese people than thin ones and a longer period expected for the return of the temperature to normal.

The color of the patient is a good index of his condition. This, together with the blood pressure and the temperature record, are three most valuable aids in indicating the patient's condition. Cyanosis of the lips, a beginning pallor especially of the face about the mouth, even if not accompanied by other changes, is a warning sign of failing peripheral circulation. It is usually followed very soon by a drop in systolic and diastolic pressure. The respiration may or may not change. If the respiration decreases in rate at such a time the temperature may rise, probably because of the reduced loss of heat by means of the expired air. A change in color (pallor) is usually accompanied by a stage of excitement, although sometimes the stage of excitement occurs first. With the onset of these symptoms, the patient should be watched very carefully, and if they continue the box is removed and the temperature returned to normal as soon as possible. The most efficient agent for this purpose is the cold enema.

The blood pressure (Fig. 8) usually rises with the elevation in temperature, although occasionally it remains at its original level throughout the treatment. If it has risen during the elevation of the fever it usually begins to fall when the patient reaches the maximum of his flush and perspiration (39° to 40° C.). It then continues to fall throughout the rest of the treatment period, and in the average patient reaches a rather constant level in the last hour of 80 mm. of mercury systolic, 60 diastolic. Occasionally in patients who already have a systolic pressure of around 100 there may be a steady fall from the beginning of the treatment. It usually reaches in such a case the low level of 70 systolic, 60 diastolic. The lowest pressure which we have seen was reached in a patient who had been chronically invalided by arthritis for a long time. She reached the astoundingly low level of 40 systolic and 30 diastolic, which she maintained for a considerable period (3 hours) without any other evidence of difficulty, and with a gradual return to a 90 systolic and 70 diastolic the next day.

In general, electrocardiograms show the decrease in voltage of the action currents of the heart consistent with a low blood pressure. While there are other changes apparent in the electrocardiograms, their exact relation is not clear.

The general reaction of the patient throughout the treatment can be improved by close attention to a great many small details. The room should be darkened. All noise should be eliminated as much as possible. A registering or indicating thermometer makes it unnecessary to disturb the patient to take the 10-minute rectal

temperatures, thus allowing him to sleep as much as possible. An atmosphere of calmness must be created by the personnel. Sedatives should be given to make the patient doze but not enough to

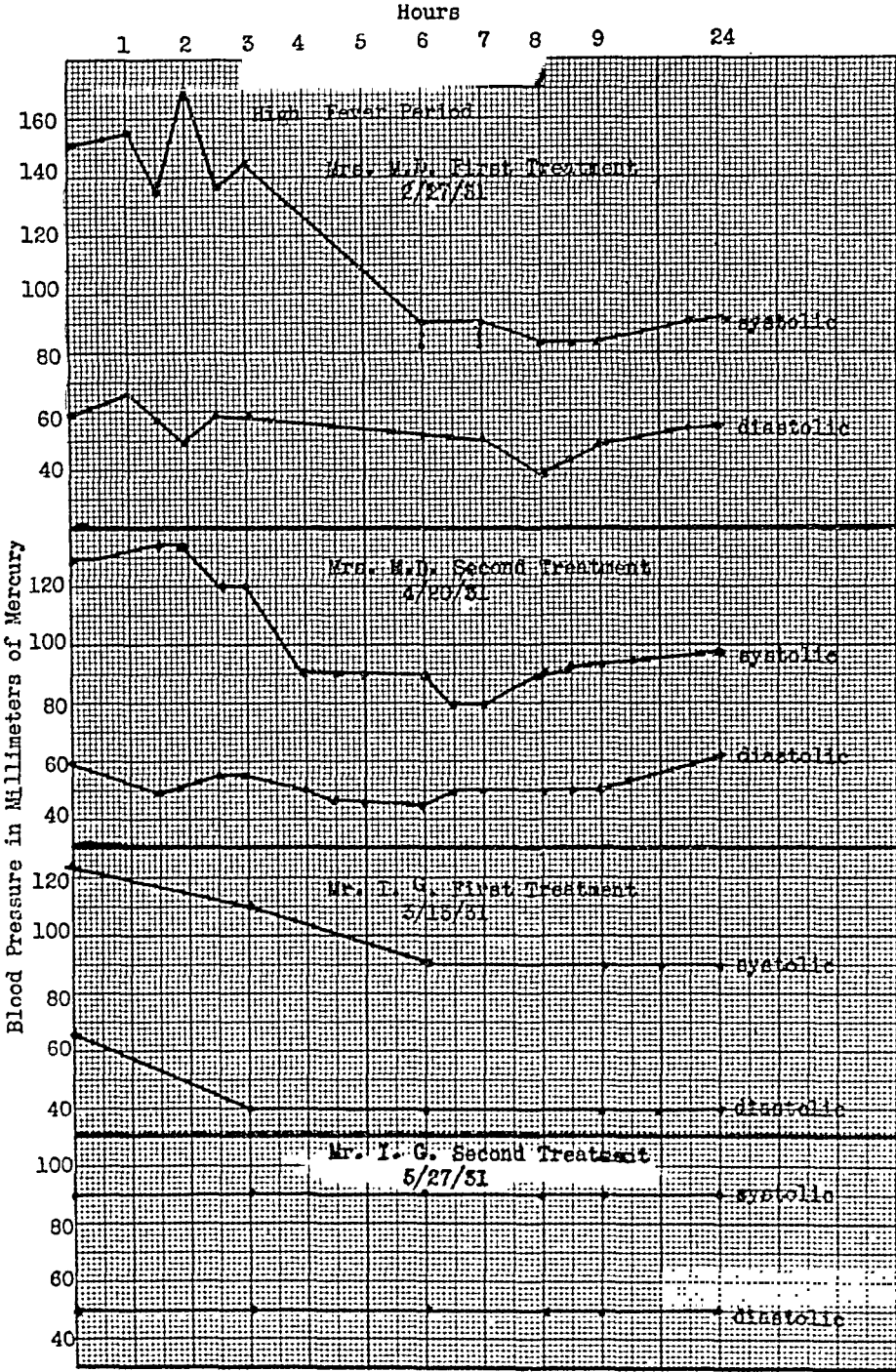


FIG. 8.—These 4 typical curves of the variations in the blood pressure cover the usual ranges. The pressure is generally lower and shows less fluctuation during the second treatment.

make it difficult to ask him questions about his sensations and to get him to drink the amount of fluid necessary to maintain the proper water balance. Two to 4 kilos of weight may be lost during the treatment from waterloss.

At the end of the treatment the patient should be lifted to his bed and not allowed to move suddenly lest vomiting occur, which may continue if once started for some hours. We have thought that paraldehyd and morphin, as well as the barbital derivatives, intensified the vomiting after treatment and even caused it to continue for 2 or 3 days. This happened too consistently to be purely

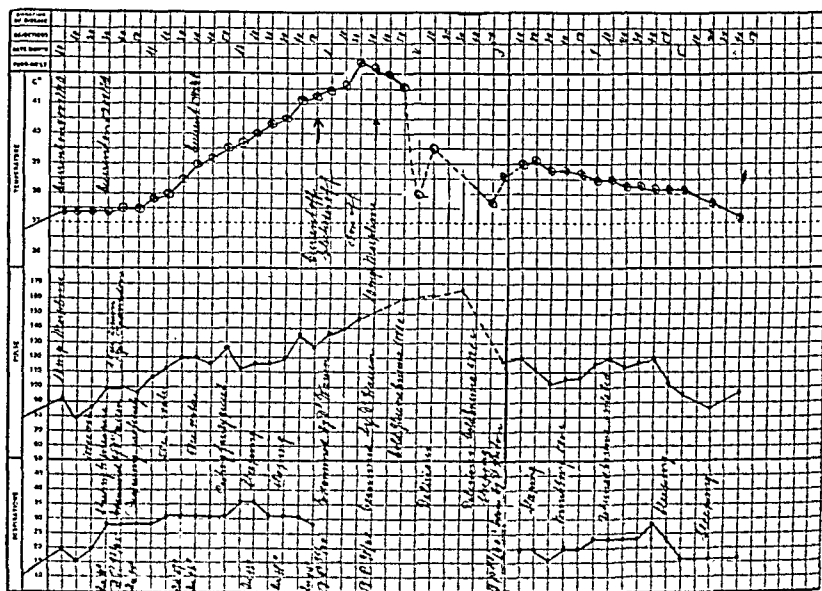


FIG. 9.—This paretic patient suddenly stopped breathing during treatment while sleeping. Artificial respiration was necessary six times during the next hour. The temperature rose to 42.4° C. The pulse and blood pressure changed very little during this period. This patient swallowed his tongue whenever his head rolled face upward. This was finally discovered and the tongue held out with a hemostat and caused no further trouble. The temperature was reduced efficiently by cooling and instilling two cold enemata. This patient is on parole (3 treatments).

circumstantial. With badly degenerated paretics who are apt to become deeply asleep or unconscious during the treatment, care should be taken that the tongue does not fall back and block the respiration (Fig. 9).

The most uncomfortable portion of the fever period for the patient occurs while the patient's temperature is at from 39° to 40° C., at which time the sedatives are usually administered. The patient is restless and feels very hot and oppressed. A slight delirium is often noted. It is a great relief to the patient when the temperature rises above 40° C., as these sensations then disappear to a great extent.

The patient relaxes and usually sleeps in short naps without further sedatives. The patient, of course, feels quite hot throughout the treatment. He is apt to feel very tired near the end of the 5-hour elevation in temperature, and unless he has been told exactly about the duration of the treatment beforehand he is apt to get somewhat restless. This can often be prevented by placing a clock where he can see it during the last hour of the treatment. It is not wise to push the sedative too much at this time, since the patients are apt to sleep soundly as soon as the temperature drops, and it would be impossible to force fluids after the treatment is over. The latter is an essential portion of the recovery period because the patient is apt to feel weak the next day if his fluid intake has not been sufficient.

The ambulatory patient in good general condition is allowed to go home by noon the day following treatment unless he comes from a considerable distance, in which case he is kept over another day. Except for nausea which could be attributed directly to the narcosis and occasionally weakness lasting for a few days, there have been no deleterious after effects. This, of course, does not include the occasional burn under the electrode. These have responded well to tannic acid dressing and usually heal in about 10 days without difficulty. They are rarely more than simple blisters. One in our series was followed by a keloid which had to be treated with radium.

Results. One hundred treatments have been given to 57 patients, from February, 1930, to August 1, 1931. The artificial hyperthermia procedure has been greatly modified and refined within this period. The method now used will give good results in careful hands with properly selected patients. We feel that the conditions under which we had to work and the type of patient whom we treated at first were not of the best. There have been 2 fatalities.

TABLE 1.—TYPES OF CASES TREATED BETWEEN FEBRUARY, 1930, AND AUGUST, 1931.

	Cases.	Treatments.
Syphilis, C. N. S. (paresis)	18	33
Arthritis, chronic (infectious and noninfectious)	15	26
Arthritis, G. C.	9	16
Vaginitis, G. C.	2	4
Meningitis, G. C.	1	3
Multiple sclerosis	3	4
Encephalitis, chronic	1	3
acute	1	1
Hypernephroma	1	3
Miscellaneous	6	7
Total	57	100

Oldest patient, aged 65 years; youngest patient, aged 3 weeks.

Case Abstracts. CASE 1.—The first fatality occurred with the second patient treated: a colored girl, aged 25 years, who had just recovered from alcoholic hallucinations. She had central nervous system syphilis and her mental status was poor. Her prescribed antisyphilitic treatment was not

consistently pursued because of her drunkenness. She rarely took treatment at the proper interval. After recovering from the delusional state she seemed to be in good general condition on physical examination. In view of this fact and the difficulty in giving her the regular form of treatment, artificial fever therapy was suggested and attempted. At that time blankets were used to prevent the patient from losing heat. These caused a sense of restraint and the patient was apprehensive about this. After a good deal of trouble with the treatment machine the temperature was finally elevated at the end of six hours to 41.5° C. by mouth thermometer and 42° C. by rectal thermocouple. This was maintained for about 1 hour, when the patient became delirious and struggled violently to get out of bed. She became short of breath. The covers were removed. She vomited a large amount of fluid, and the pulse and respiration stopped. The patient could not be resuscitated. The pulse rate at its highest was 170 per minute and the respiration 45. At autopsy there were small hemorrhages in the epicardium such as are seen after sudden death, a somewhat enlarged thymus, and no obvious cause to account for the sudden exitus. The final diagnosis was chronic alcoholism, central nervous system syphilis, hypertrophy of the thymus. After much discussion it was concluded that chronic alcoholism was the major factor in the demise of this patient.

CASE 2.—The second fatality occurred almost exactly 1 year later. This patient was a white woman, aged 26 years, with a diagnosis of chronic encephalitis lethargica, with symptoms of 8 years' duration. She had been steadily going down hill in spite of various therapeutic measures. Among other symptoms, the patient was subject to attacks of noisiness, screaming and crying, with seizures of twitching of the extremities, vertical nystagmus and incontinence, lasting 24 to 48 hours. These attacks were repeated at intervals of from 2 to 3 days, and had increased in severity and number during the last 6 months of her life. The patient was given an artificial fever treatment on February 27 and another on April 20, 1931, with marked improvement in the symptoms. A third treatment was started on May 20. The temperature rose in the same manner as it had on the previous occasions, and the current was shut off at the end of 2 hours, when the temperature had reached 41° C. The temperature then rose to 41.5° C. in the usual manner. Suddenly the patient began to have one of her usual attacks except that it was of marked severity. The blood pressure began to drop, and within about 1 hour had fallen from 100 systolic and 60 diastolic until it could no longer be measured. The radial pulse was not palpable. The heart rate continued unchanged. The sounds were of good quality. The color, of course, changed to a pallor. The respiration became slower and slower and finally irregular. The head was lowered and various medications tried without effect. The temperature began to rise steadily as the respiratory rate decreased, and when the respiration had almost completely ceased the temperature reached 43° C. The patient was put in an ice pack and given an ice cold enema which was not retained. Various mixtures of oxygen and carbon dioxide were successful in stimulating the respiration for about $1\frac{1}{2}$ hours after this. There was very little cyanosis as long as the respiration and heart rate were maintained. When the respiration began to fail, in spite of the oxygen and carbon dioxide mixture, the patient was put in a Drinker respirator. The heart was failing, and it stopped entirely by the time that the neck piece of the respirator was adjusted. The temperature had fallen to 40° C. before the heart stopped.

Autopsy showed no variation from the normal in any of the organs except for the few epicardial hemorrhages such as are commonly seen in acute exitus. The heart was otherwise in good condition; the muscle well developed. It was not dilated. The brain showed no gross or microscopic lesions on careful search. The results of studies with special stains are not

yet available for report. Chemical analyses made on the heart's blood 1 hour after exitus showed: Nonprotein nitrogen, 43 mg. per 100 cc.; chlorid, 460 mg.; sugar, 95 mg. per 100 cc.; hematocrit, red blood cell content, 51 per cent. In other words, there is no evidence from the data at hand to explain the cause of death.

This case illustrates the rise in temperature coincident with the drop in the respiration rate. The failure of the circulation to maintain the blood pressure was probably due to the peripheral dilatation which did not respond to the usual stimuli. The ice packs failed to be of use either in bringing down the temperature or in raising the blood pressure by contracting the peripheral vessels of the skin. A continuous cold enema seems to have been the most effective agent in bringing the temperature down from the high point to 40°. The period above 41.5° was approximately 15 minutes in duration, which of itself should not have been the cause of death. The fall in pressure and the failure of the respiration were apparently the main contributing factors.

It is felt that the first fatality could have been avoided if the treatment had been conducted with the present technique. The possibility of damage to the respiratory mechanism in patients having central nervous system lesions increases the risk of treatment in such cases. All those concerned realized before treatment that the patient with the chronic encephalitis was a very bad risk. The treatment of similar cases should be undertaken with caution.

In summarizing our experience with 100 treatments of 57 patients having various diseases, we feel that the contraindications for treatment are somewhat similar to those which would hold for an abdominal surgical operation. Chronic alcoholism and obesity, arteriosclerosis with its possibility of a ruptured vessel in case the pressure should rise too high during the first stages of the fever, central nervous system lesions involving the respiratory mechanism, cardiac damage with lowered cardiac reserve are all specific contraindications. The blood pressure readings still remain the simplest index of the efficiency of the vascular system during treatment.

Preliminary Clinical Results. The first patients treated were chosen from a group of badly disoriented and degenerated paretics. Some of these were in very bad physical condition. Two who were especially disintegrated, and who had been in bad physical condition for many months, were given artificial fever and tryparsamid, but they continued to go down hill and died several months after the fever treatment. The rest have shown great clinical (Fig. 10) and psychic improvement and gains in weight of from 20 to 30 pounds. All have been paroled, and of the 14 only 1 has relapsed, but this patient has had only 1 treatment of a 5-hour fever. The remainder have had from 2 to 4 treatments at intervals of from 10 days to several months apart. The chemical changes have been consistent and resemble the changes after malarial therapy. The

gold sol. curves, the protein and the number of cells in the spinal fluid returned to the normal. The Wassermann reactions in the spinal fluid and blood have changed somewhat but have not yet become negative. The shortest period between treatment and parole was 5 months, the longest 9 months.

Elizabeth Kiehle 2/6/30 Elizabeth Kiehle 5/20/30
 Kiehle Before Treatment Elizabeth Kiehle 10/26/30
 Elizabeth Kiehle 2/7/30 Elizabeth Kiehle 12/17/30

FIG. 10.—This group of signatures illustrates the subsidence of the ataxia in a paretic patient after four artificial fever treatments. The patient is on parole.

The next series treated was an arthritic group. In this group those who responded most were patients suffering with arthritis of gonorrheal origin. The acute lesions subsided rapidly, lost their redness and tenderness, and there was gradual recovery from the stiffness. The chronic lesions became painless and there was gradual relief from the stiffness, with increased mobility. Two treatments were given from 10 days to a month apart. The effectiveness of the 5-hour fever period in gonorrheal infection is supported by water-bath experiments on the thermal death time of gonorrheal cultures, the results of which will be reported elsewhere. A series of patients with chronic infectious arthritis with soft tissue proliferation and bone atrophy or with joint destruction was treated next. Immediate relief from pain occurred and in some patients joint pain has not returned within a period of 8 months. There has been increased mobility (Figs. 11 and 12) and a reduction in the size of the soft tissue swelling. As the patients have used their joints more, some of them have been troubled with muscle pains. The usual rehabilitatory measures are, of course, necessary after the fever treatment. It is too early to speak of the permanent results in arthritis at this time. This will be reported elsewhere at a later date.

Gonorrheal vaginitis and cervicitis in adults has been cleared up in from 1 to 2 treatments with no evidence of infection by

culture or smear after the next menstrual period following treatment. These cases had all been resistant to the usual forms of therapy.

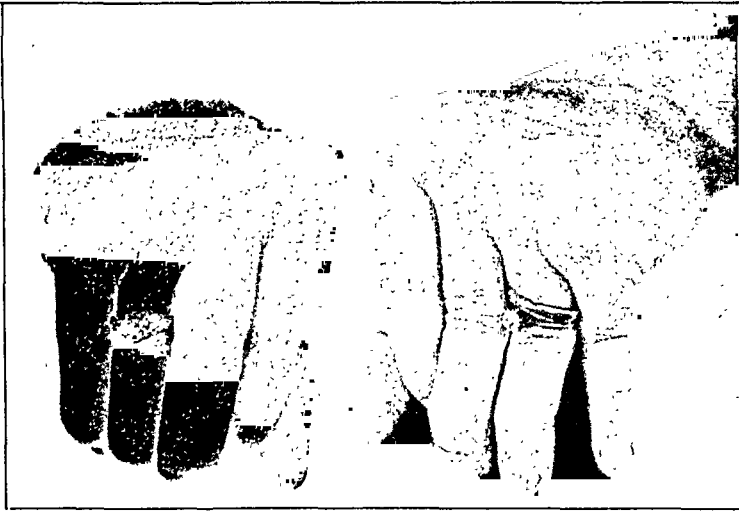


FIG. 11.—The appearance of the hands of a 50-year-old patient with advanced arthritis. This shows the maximum extension before treatment.

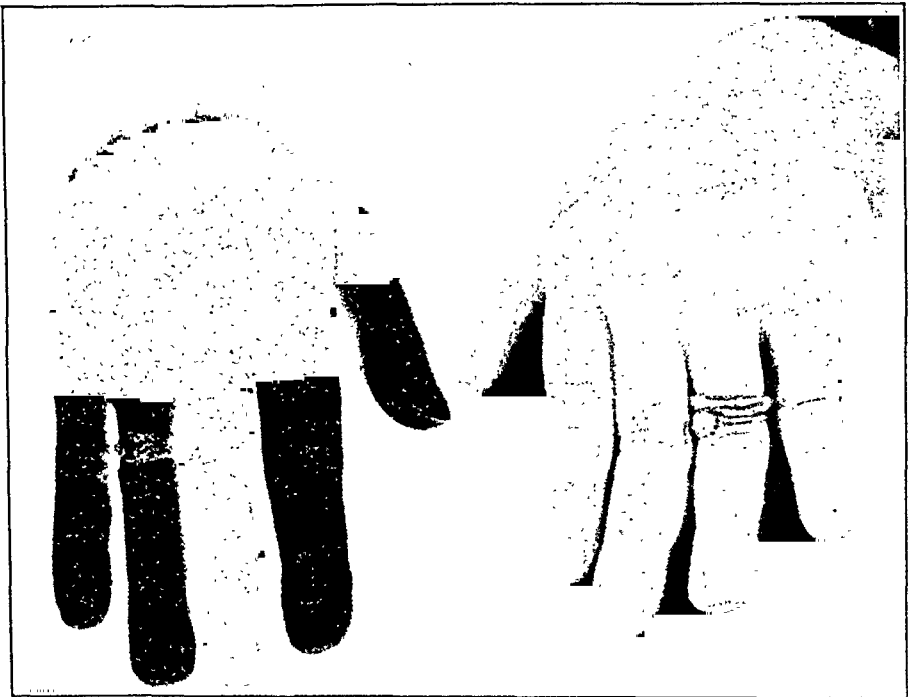


FIG. 12.—The hands of the same patient 1 month after fever treatment showing the increased mobility of the joints. This has been retained for 7 months.

Other disease entities have also been treated, but the number has been too few and the time too short to draw any conclusions from these cases. We wish to emphasize that the above statements are tentative and are based upon periods of observation of relatively short duration, the longest that the patients have been under observation being only $1\frac{1}{2}$ years. It can be stated definitely that immediate clinical improvement in the paretic group, certain types of the arthritic group and the group having gonorrheal infections is very encouraging. How lasting these results will be can only be determined by observations over a longer period of time.

Summary. Artificial hyperthermia can be carefully and accurately controlled by a rather standardized procedure well within the scope of the average hospital. The whole body temperature is elevated by the passage of high frequency currents through the trunk by means of large block-tin electrodes. The temperature is maintained at any desired level below 42° C. for 5 hours without danger to a patient in ordinary physical condition. This is accomplished by keeping the patient surrounded by air at a temperature sufficiently high to compensate for losses by radiation, etc. The temperature can be lowered at will by cooling the patient's environment, by cold drinks and, most important, by a cold enema. The condition of the patient is determined by temperature, pulse and respiration readings taken every 10 minutes, by blood pressure determinations at frequent intervals, and by noting the color of the skin. The fluid balance should be maintained. Excitement is avoided by proper sedatives and calmness on the part of the personnel.

One hundred treatments have been given to 57 patients in 19 months, with a mortality of 2 per cent, based on 100 treatments; if based on the number of patients then the mortality is 3.5 per cent.

A careful selection of patients should be made until sufficient experience with the method of treatment by artificial hyperthermia has been acquired to evaluate the possibility of damage to patients in poor condition.

NOTE.—We wish to express our great appreciation for the coöperation of the various members of the clinical services who have referred these cases to us for treatment. Especial thanks are due to Dr. William S. McCann, Chief of the Medical Service; Dr. J. R. Murlin, Director of the Department of Vital Economics; Dr. Eric Clarke, in charge of the Division of Psychiatry; Dr. F. D. Streeter, Clinical Director of the New York State Hospital; Dr. R. Plato Schwartz, in charge of Orthopedies, and Dr. Charles Carpenter for their suggestions and criticisms of the method of treatment; Dr. G. H. Whipple and Dr. W. B. Hawkins for their very careful postmortem study of the 2 fatal cases; Dr. W. R. Whitney, Director of Research of the General Electric Company for a great deal of technical advice and interest in the methods used; Mr. A. Page, of the General Electric Company, and Mr. H. E. Gordon, of the Rochester Telephone Corporation, for many helpful suggestions; Mr. Charles Renaud, of the General Electric X-Ray Corporation, for the loan of certain equipment. This work has been supported by a special grant from the Rockefeller Foundation.

BIBLIOGRAPHY.

1. Nasset, E. S., Bishop, F. W., and Warren, S. L.: Physiological Effects of High Frequency Currents: I. Respiratory Metabolism and Certain Changes in the Blood of Anesthetized Dogs, *Am. J. Physiol.*, 1931, **96**, 439.
2. Carpenter, C. M., and Hinsie, L.: Radiothermic Treatment of General Paralysis, *Psychiat. Quart.*, 1931, **5**, 215.
3. King, J. C., and Cocke, E. W.: Therapeutic Fever Produced by Diathermy: Application in Treatment of Paresis, *South. Med. J.*, 1930, **23**, 222.
4. Neymann, C. A., and Osborne, S. L.: Treatment of Dementia Paralytica, with Hyperpyrexia Produced by Diathermy, *J. Am. Med. Assn.*, 1931, **96**, 7.

BACILLUS PROTEUS SEPTICEMIA WITH RECOVERY.

BY H. V. PARYZEK,

AND

E. E. ECKER,

CLEVELAND.

(From the Institute of Pathology and Maternity Hospital, Western Reserve University.)

ALTHOUGH *Bacillus proteus* is often associated with a multitude of inflammatory conditions in man, its occurrence in septicemias and bacteremias is extremely rare. As early as 1902 Berthelmann and Mau¹ reported its presence in the blood stream of a case of urethral fever and pyelonephritis. Since this publication, case reports have appeared from the hands of Jochmann,² Lenhartz,³ Goebel,⁴ Maymone,⁵ Reye,⁶ Warren and Lamb,⁷ and Irimonoiu and Popa.⁸ In the case of Warren and Lamb, the antemortem blood culture showed an unidentified Gram negative bacillus while the postmortem cultures yielded an organism of the *B. proteus* group. Irimonoiu and Popa's organism was also obtained at autopsy. Most authors agree that the organism is rarely recovered during life. In view of the rarity of the infection, we desire to present an unusual case of *B. proteus* septicemia with recovery.

Case Report. Patient R. D. F., aged 24 years, primipara, was referred to us through the courtesy of Dr. J. T. Smith, Jr., July 15, 1931. She was admitted to Maternity Hospital July 9, 1931, for the purpose of inducing labor, since the child was too large for the contracted pelvis. A Voorhees' bag was inserted July 10, 1931, at 11.45 p.m. and was expelled 8 hours later. Labor began about 3 hours after induction, and was completed by podalic version after manual dilatation July 11, 1931, at 11.45 p.m.

The pregnancy was uneventful and at no time were there any symptoms suggestive of genitourinary disease. A short time prior to delivery the patient began having an irregular temperature ranging from 38° to 39° C. (see temperature chart). This continued until the fourth postpartum day, when she had three very severe chills, which were followed by a temperature of 40° C. An irregular, septic type of temperature, accompanied by

frequent chills and drenching sweats continued for 60 days. The chills were of unusual severity, lasting from 30 to 60 minutes. Apart from a feeling of exhaustion the patient was apparently comfortable during the remissions in fever.

Physical Examination. A well-developed, well-nourished young female apparently comfortable. Her skin was moist, and without pallor. Pupils were equal and reacted normally to light and accommodation. Teeth were well preserved. The tongue was moist and slightly coated. Lungs revealed no abnormalities. The cardiac dullness was normal, and normal sounds unaccompanied by murmurs were elicited by auscultation. Abdomen was slightly distended, not tender. Uterus was palpable in lower abdomen, not tender and apparently involuting satisfactorily. Liver and spleen were not palpable. No tenderness in the region of the kidneys. Reflexes were normal. *Lochia* were normal.

Laboratory Tests. Urinalysis revealed albumin (1 +), with numerous pus cells and bacteria. White blood cells, 6400. Urine culture was positive for *B. coli*. Blood culture was negative after 72 hours. Routine treatment for pyelitis was instituted but no definite improvement took place.

Course. July 17, 1931, the abdominal distention increased and was accompanied by tenderness in the right flank and lower right quadrant. No mass was palpable. Three days later the distention lessened, and a hard, irregular, slightly tender mass was palpable to the right of the uterus. Vaginal examination revealed a firm, nonfluctuating, irregular ovoid mass quite high off the right cornu, which was sensitive at a point over the scar of a former appendectomy. The fundus was in the midline, and showed normal involution. The mass gradually disappeared in 2 weeks. Urine continued to show varying amounts of albumin with numerous pus cells and bacteria. A residual urine averaging 150 cc. was noted at this time.

Cystoscopic examination revealed a severe degree of cystitis. Both ureters were slightly edematous and were catheterized without difficulty. A steady flow was obtained from the right side, and an intermittent flow from the left. Bladder urine showed numerous pus cells. Right kidney urine showed 8 to 10 white blood cells, the left 4 to 6 white blood cells per high-power field. Cultures revealed *B. coli*. A retention catheter was inserted. At this time the blood leukocyte count ranged from 15,000 to 27,000, with a gradually developing secondary anemia. Red blood cell 3,890,000. Hemoglobin 62 per cent (Sahli).

August 4, patient was transfused with 250 cc. of whole blood. This was followed by a slight improvement in the red count, without any change in the clinical course. Fever and chills continued, and the patient began showing more marked exhaustion, with anorexia and mental depression. Transfusion of 500 cc. of whole blood was repeated August 12 and August 16. Repeated urine cultures revealed the presence of *B. coli*. Blood cultures at this time were negative.

August 15, there was swelling and tenderness of the left ankle, which gradually spread to the calf and thigh, with an apparent increase in the general reaction. September 3, 1931, left thigh was slightly edematous, and no tenderness was present. Abdomen was soft, not tender, spleen and liver not palpable. Vaginal examination revealed a normal uterus, without any inflammatory masses in the adnexa. Urine showed a negative albumin with fewer pus cells and bacteria. Red blood cells, 4,690,000. White blood cells, 16,700. Hemoglobin, 70 per cent (Sahli). Differential: Polymorphonuclears, 84.5 per cent; large lymphocytes, 1 per cent; small lymphocytes, 6.5 per cent; transitional cells, 7.5 per cent; basophilic cells 0.5 per cent.

September 5, little change was noted in the patient's condition. A new blood culture revealed the presence of *B. proteus*. The patient's blood

agglutinated the organism in a dilution of 1 to 640. At this time a definite change in the clinical course was noted. The chills became less frequent, remissions in temperature lasted 24 to 36 hours, and there was a gradual decline by lysis.

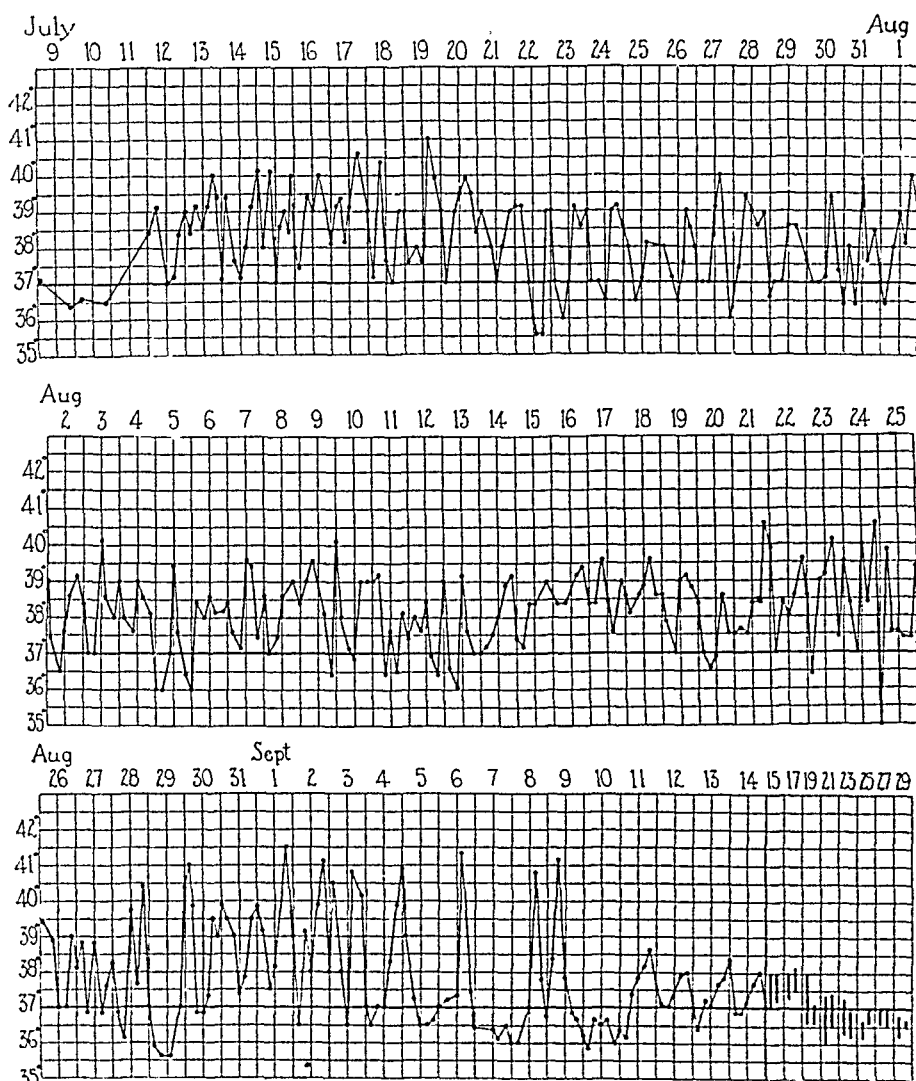


FIG. 1.—Temperature chart from admission to discharge. Noon of each day is indicated by the vertical line midway between the date figures. For the last 16 days, only maximum and minimum figures are given. Here each vertical space represents 2 days. Pulse was proportional to temperature.

The urine was clear and albumin free, with very few pus cells and bacteria. Red blood cells, 4,710,000; white blood cells, 8800. Hemoglobin, 70 per cent (Sahli). The patient was discharged from the hospital September 19, to continue her convalescence at home. Apart from the three blood transfusions and supportive medication no other therapeutic measures were instituted.

Bacteriologic Findings. The blood was drawn at the beginning of a chill, and cultured on brain broth. Incubation at 37° C. for

24 hours yielded a pleomorphic Gram negative and motile rod which gave a smooth, spreading growth (H form) on blood agar plates. The sugar reactions were as follows:

Sugars	Acid	Gas
Glucose	+	+
Galactose	+	+
Levulose	+	Slight in 72 hours.
Glycerol	+	Slight in 72 hours.
Xylose	+	+
Dextrin	± in 72 hours	—
Adonitol	± in 72 hours	—
Arabinose	± in 72 hours	—
Inulin	± in 72 hours	—
Salicin	± in 120 hours	—
Lactose	—	—
Saccharose	—	—
Maltose	—	—
Mannite	—	—
Dulcitol	—	—
Starch	—	—
Raffinose	—	—

Milk was peptonized and gelatin was liquefied. Indol was not produced and the organism bleached litmus. On Wilson and Blair's medium, the organism failed to reduce sulphite to sulphides in the presence of glucose. Acetylmethylcarbinol was not produced. The organism hemolyzed human blood and killed mice both by subcutaneous and intraperitoneal injections. From a previous blood culture, which appeared hemolyzed, we were able to isolate the same organism. The organism therefore was found in two distinct blood cultures. As stated before, the patient's serum typically agglutinated the organism in a dilution of 1 to 640. On September 5th, the patient's serum markedly agglutinated the organism in dilution of 1 to 1280. The organism was also typically and to titer agglutinated by an antiproteus serum (1 to 1280). The organism therefore belongs to the *B. proteus* group (species *mirabilis*).

Conclusions. An organism of the *B. proteus* (*mirabilis*) group was isolated from a case of postpartum septicemia of several weeks' duration. Except for the presence of a phlebitis no other complications were noted. The patient made an uneventful recovery.

BIBLIOGRAPHY.

1. Bertlesmann, R., and Dr. Mau. Münch. Med. Wehnschr., 1902, **13**, 521.
2. Jochmann, G., and Kantorowicz, A.: Zeitschr. f. Klin. Med., 1908, **66**, 153.
3. Lenhartz, H.: Nothnagel spez. Path. u. Therapie, **3**, Virchow's Archiv f. path. Anat., 1923, **246**, 443.
4. Goebel, F.: Deutsch. Archiv f. klin. Med., 1914, **116**, 119.
5. Maymone, B.: Ann. d'Igiene, 1917, **27**, 218.
6. Reye: Biol. Verein. Hamburg (quoted by Lenhartz), 1922.
7. Warren, S., and Lamb, M. E. J.: J. Med. Res., 1923-1924, **44**, 375.
8. Irimonoiu, G., and Popa, R.: Compt. rend. Soc. de biol., 1925, **92**, 1082.

THE EFFECT OF EXERCISE ON HUMAN ERYTHROCYTES.

BY CHRISTIANNA SMITH, PH.D.,

ASSOCIATE PROFESSOR OF ZÖÖLOGY,

AND

KATHARINE F. KUMPF, M.A.

SOUTH HADLEY, MASS.

(From the Walter H. Merriam Laboratory, Department of Zoölogy, Mount Holyoke College.)

THE rapid increase of erythrocytes in the peripheral blood after short periods of exercise has been confirmed many times in studies on normal variations in the numbers of red-blood corpuscles.¹ The related problems of the changes in total hemoglobin content, volume percentage, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration after marked exertion have been investigated less often. The data presented in this paper indicated that immediately after 2-minute periods of hard exercise, the total numbers of erythrocytes rose to a peak and fell to their normal average in about 45 minutes. This marked rise in numbers was not accompanied by significant variations in total hemoglobin content, volume percentage or concentration of the hemoglobin in the cells, with the methods employed for their determinations. Real decreases in values appeared, however, immediately after exercise in the mean corpuscular hemoglobin content and in the mean corpuscular volume (Table 1).

Method. The 40 experiments reported here were grouped into 3 series of 10 studies each, made on 3 persons respectively, and 1 series of 10 on 10 different individuals. All subjects were healthy young women between the ages of 20 and 35 years. Only 2 of the 13 persons under observation were accustomed to severe exertion.

The course of the investigation was the same in each of the 40 studies. A 2-minute period of hard exercise in the nature of running up and down 3 flights of stairs twice (21 steps each; height, $7\frac{1}{2}$ inches; flights set at an angle of 31.7 degrees) provided the exertion in all but 2 instances. In these 2 cases a series of exacting "setting up" exercises during a 5-minute period were used. Before the activity, blood samples sufficient to yield the determinations considered below were taken from the finger tip of the subject. The data obtained from this preliminary group of "counts" constituted the normal condition of the red corpuscles of that individual. Immediately after the exercise (no interval allowed) a second sampling was obtained and additional ones were made every 15 minutes thereafter until a total of 8 had been recorded (Table 2).

Six determinations were made from each group of samples and were obtained in the following manner:

1. *Total Red Count.* The drop of blood from the finger tip was diluted with Hayem's solution in a U. S. certified pipette. After a

thorough mixing of the corpuscles by placing the pipette in an electric agitator, the number of erythrocytes in 160 small squares (2 chambers) was recorded.

TABLE 1.—THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN THE DETERMINATIONS BEFORE AND AFTER ACTIVITY (CALCULATED FROM ORIGINAL DATA).

	Mean.	Standard deviation.	Coefficient of variation, per cent.	Probable error of mean.	Difference of means.	Probable error of difference of means.	Significance of difference.*
Total red count:							
Before	4,440,000	713,000	16	±75,000			
After	4,990,000	317,000	6.3	±34,000	550,000	±82,000	+
Hemoglobin, grams:							
Before	14.28	0.78	6.8	±0.08			
After	13.93	0.89	7.5	±0.10	0.35	±0.13	—
Volume, per cent:							
Before	39.8	2.4	6	±0.2			
After	40.7	3.2	7.8	±0.3	0.09	±0.04	—
Mean corpuscular hb., micro-							
micrograms:							
Before	31.46	1.61	5.1	±0.17			
After	28.71	2.08	7.2	±0.22	2.75	±0.28	+
Mean corpuscular volume, c.μ							
Before	89.80	5.43	6	±0.59			
After	81.93	7.22	8.8	±0.79	7.85	±0.99	+
Mean corpuscular hb. concen-							
tration, per cent:							
Before	35.11	1.93	5.5	±0.21			
After	35.15	2.47	7	±0.27	0.04	±0.36	—

* "Unless a deviation is more than four times its probable error, there is no great reason for thinking it may not result from pure chance."

2. *Total Hemoglobin.* The blood sample was drawn into a hemoglobin pipette and diluted with a 1 per cent solution of hydrochloric acid. After intervals of 20 minutes or more readings were made in a dark room with a Duboscq colorimeter provided with a Bausch and Lomb-Newcomer hemoglobin attachment. In all instances the values were read with light from an 8-inch Corning daylight lamp. The determinations expressed in grams per 100 cc. of blood were the averages of at least 5 readings of each sample. As these readings were too low, 2.48 gm. per 100 cc. were added, the correction figure having been obtained by previous comparison with the measurement of the hemoglobin content of blood by the van Slyke apparatus.

3. *Volume Percentage.* The blood was prepared for study in van Allen hematocrit tubes according to the methods suggested by that author.^{2,3} A 1.3 per cent solution of sodium oxalate was used as the most satisfactory diluent. The tubes were sealed with padded rubber bands and then centrifuged at a speed of 4000 revolutions per minute (radius of arm, 7 cm.) until 2 consecutive readings made at 5-minute intervals yielded the same value. In every case the centrifuging continued for at least 30 minutes. The column of

packed erythrocytes was read in terms of the percentage of the total original column (*e. g.*, corpuscles 40 per cent of total volume of sample).

TABLE 2.—DATA FOR RED-CELL VALUES FOR THE 4 SERIES OF 10 EXPERIMENTS EACH, BEFORE AND AFTER A 2-MINUTE PERIOD OF HARD EXERCISE.

	Before activity.	After activity.	15 min.	30 min.	45 min.	60 min.	75 min.	90 min.
<i>1. Total Erythrocyte Counts (Millions).</i>								
Subject H . . .	4.29	4.70	4.68	4.34	4.29	4.29	4.28	4.29
Subject K . . .	4.67	5.17	4.99	4.71	4.66	4.64	4.65	4.65
Subject G . . .	4.26	4.81	4.72	4.35	4.27	4.26	4.27	4.27
10 persons . . .	4.54	5.32	4.90	4.64	4.57	4.54	4.53	4.53
Average	4.44	5.00	4.82	4.51	4.45	4.43	4.43	4.44
(40 experiments)								
<i>2. Total Hemoglobin (Grams).</i>								
Subject H . . .	14.0	14.7	14.4	14.1	13.7	13.8	13.5	13.5
Subject K . . .	14.3	14.4	14.2	14.2	14.3	14.2	14.3	14.2
Subject G . . .	13.1	13.2	13.3	13.1	13.2	13.1	13.1	13.0
10 persons . . .	14.4	14.9	14.7	14.4	14.4	14.3	14.4	14.4
Average	14.0	14.3	14.2	14.0	13.9	13.9	13.8	13.8
<i>3. Total Volume (Per cent).</i>								
Subject H . . .	40.8	42.2	41.4	40.7	41.0	42.1	40.7	41.9
Subject K . . .	41.0	42.2	41.9	40.9	41.3	41.1	41.4	42.2
Subject G . . .	37.7	38.0	38.1	36.7	37.6	37.2	37.0	37.4
10 persons . . .	39.8	40.6	40.0	39.3	39.2	39.6	39.4	39.6
Average	39.8	40.8	40.4	39.4	39.8	40.0	39.6	40.3
<i>4. Corpuscular Volume (Cubic Micra).</i>								
Subject H . . .	95.0	89.9	88.6	93.9	95.5	98.2	94.9	97.6
Subject K . . .	87.9	81.5	84.5	86.8	88.7	88.5	89.1	90.6
Subject G . . .	88.4	78.9	80.8	84.2	88.0	87.2	86.5	87.6
10 persons . . .	88.0	77.5	81.9	85.0	86.2	87.3	87.1	87.0
Average	89.8	82.0	84.0	87.5	89.6	90.3	89.4	90.7
<i>5. Corpuscular Hemoglobin (Micromicrograms).</i>								
Subject H . . .	32.6	31.3	30.8	32.5	31.9	32.2	31.5	31.5
Subject K . . .	30.6	27.9	28.5	30.2	30.7	30.6	30.8	30.5
Subject G . . .	30.8	27.4	28.2	30.1	30.9	30.8	30.7	30.4
10 persons . . .	31.7	28.0	30.0	31.0	31.5	31.5	31.8	31.8
Average	31.4	28.7	29.4	31.0	31.3	31.3	31.2	31.1
<i>6. Corpuscular Hemoglobin (Concentration, Per cent).</i>								
Subject H . . .	34.3	34.8	34.8	34.6	34.3	32.8	33.2	32.2
Subject K . . .	34.9	34.1	33.9	34.7	34.6	34.6	34.5	33.7
Subject G . . .	34.8	34.7	34.9	35.7	35.1	35.2	35.4	34.8
10 persons . . .	36.2	36.7	36.8	36.6	36.7	36.1	36.6	36.4
Average	35.1	35.1	35.1	35.4	35.2	34.7	34.9	34.3

4. *Mean Corpuscular Volume.* The average size of a red corpuscle was calculated by the use of Wintrobe's⁴ formula:

$$\begin{aligned} \text{Corpuscular volume (cubic micra)} &= \frac{\text{Volume of packed cells (cc. per 1000 cc.)}}{\text{Total red-cell count (millions per cu.mm.)}} \\ c. g., \frac{400}{4.4} &= 90.9 \end{aligned}$$

5. *Mean Corpuscular Hemoglobin.* The average amount of hemoglobin in a single cell was determined by using the formula employed by Wintrobe:⁴

$$\begin{aligned} \text{Corpuscular hb. (micromicrograms)} &= \frac{\text{Total hb. (gm. per 1000 cc.)}}{\text{Total red-cell count (millions per cu.mm.)}} \\ c. g., \frac{140}{4.4} &= 31.8 \end{aligned}$$

6. *Mean Corpuscular Hemoglobin Concentration.* Since the proportion of hemoglobin in relation to other corpuscular contents was considered as important as the quantity in each cell this final set of calculations was made according to the following equation:⁴

$$\begin{aligned} \text{Corpuscular hb. concentration (in per cent value)} &= \frac{\text{Total hb. (gm. per 100 cc.)} \times 100}{\text{Volume in cc. per 100 cc.}} \\ c. g., \frac{1400}{40} &= 35.0 \end{aligned}$$

Preliminary experiments were performed in each type of technique to ensure satisfactory accuracy in the accumulation of the data.^{5,6}

Results. 1. *Total Red Count.* The pattern of the curve in Chart I showed marked increase in the number of erythrocytes immediately after exercise (average increase of 550,000 cells) and a gradual return to normal within a period of 30 to 45 minutes. In subject H, the second and third points were nearly alike and the maintenance of these high values was followed by a fairly abrupt drop to the normal level. Each separate experiment on this individual presented a picture of the same type. The series on subject G showed a tendency toward the same sort of pattern but, in general, it might be said that in subjects K, G and 10 persons there was no evidence of a plateau as in subject H, and the drop in total number was marked and progressive within the first 15 minutes after exercise (Table 2).

2. *Total Hemoglobin.* The amount of hemoglobin in the blood was slightly but not significantly increased by exercise (Chart I, Table 1). There was an early return to normal values. The hemoglobin content in the H series had a more decided rise immediately

after exercise and, unlike the other 30 experiments, dropped below normal and maintained itself at this lower level (Table 2).

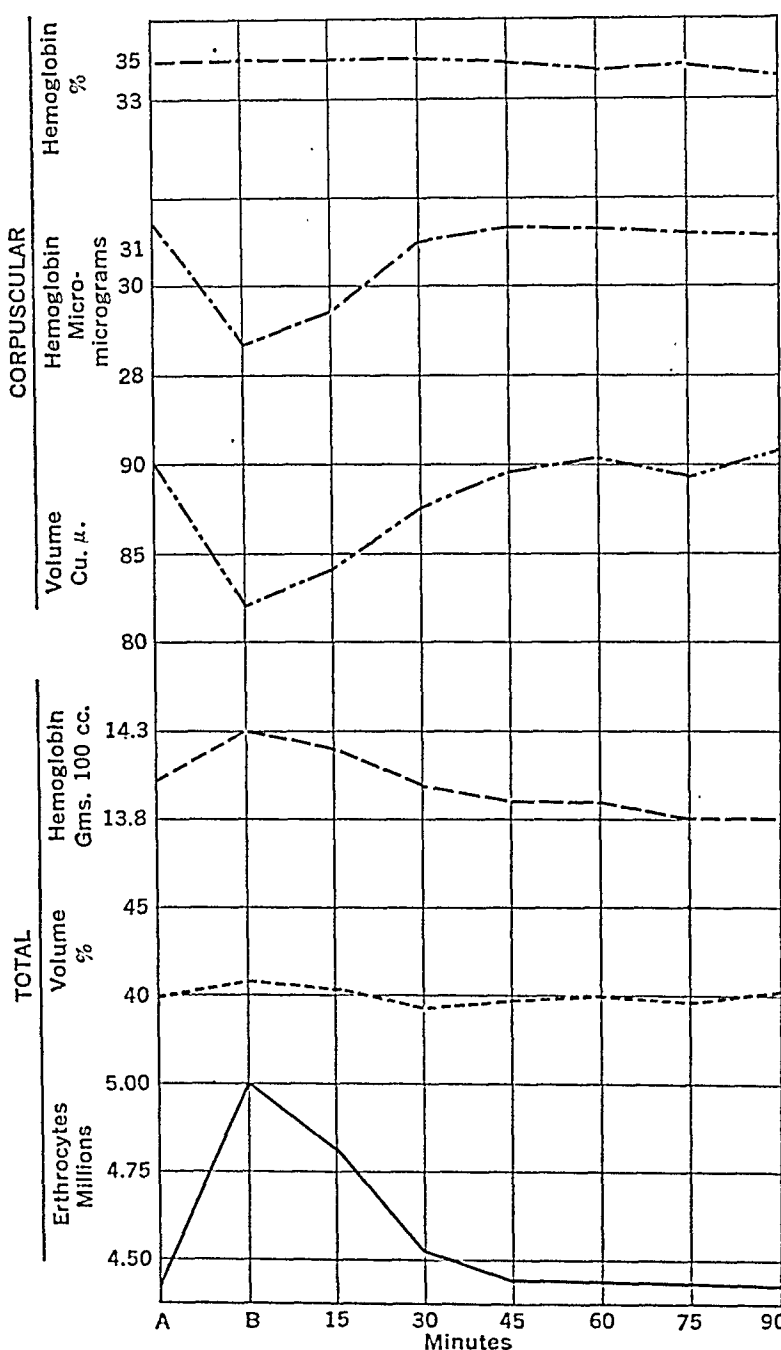


CHART I.—Composite curves, 40 experiments. The effect of 2-minute periods of exercise on red-cell values. A, before exercise; B, immediately after exercise.

3. *Volume Percentage.* The volume percentage changed but little (Chart I, Table 1). Separate experiments exhibited some variations in results and occasionally actual drops in volume percentage occurred following activity; however, in 31 of the 40 cases there was a slight increase or an unchanged condition.

4. *Corpuscular Volume.* The estimated corpuscular volume (the total cell volume per unit of blood divided by the total number of cells per unit of blood) dropped immediately after exercise and regained its normal values in $\frac{3}{4}$ to 1 hour (Chart I, Table 1).

5. *Corpuscular Hemoglobin.* The estimated corpuscular hemoglobin (the amount of hemoglobin per unit of blood divided by the number of corpuscles per unit of blood) paralleled the drop in corpuscular volume (Chart I, Table 1). Without exception there was a real decrease in the average amount of corpuscular hemoglobin immediately following the period of activity. The lowest value was attained at the second point in 3 of the groups and at the third point in the series on H (Table 2). The return to normal was simultaneous with a similar recovery of the total number of corpuscles and was likewise maintained to the end of the experiment with the exception of subject H.

6. *Corpuscular Hemoglobin Concentration.* The constancy of the proportion of hemoglobin in a cell during and after strenuous activity is well shown in Chart I and Table 1.

Discussion. As in most of the previous work on the effect of a short period of strenuous exercise on red blood corpuscles, the present study revealed a significant increase in the total number of erythrocytes ($550,000 \pm 82,000$, Table 1). Sometimes the actual change following exertion was as low as 130,000 cells (Case 7, original data). This slight variation may be contrasted with such a marked response as a rise of 1,200,000 corpuscles (Case 36, original data). The return to the initial number of cells occurred within 45 minutes after exertion and was maintained to the end of the experiment.

The hemoglobin content of the blood, on the other hand, presented no significant increase as a result of exercise (0.35 ± 0.13 gm., Table 1), although a slight rise in the pattern of the curve (Chart I) could be seen. Considered separately, the experiments were characterized by considerable variation. These deviations may be due to uncontrolled variables in technique, such as many other workers in this field have experienced. The second count was less than the normal value in 9 cases with a maximum fall of 0.48 gm. (Case 13). One experiment showed no change at all after exercise (Case 7). In 30 (75 per cent) of the studies the B count was above the normal hemoglobin content, the maximum increase being 2.06 gm. (Case 5). This failure of the hemoglobin values to follow the pattern of the curve for red-cell numbers (Chart I) seemed to corroborate the work of Schmaltz (quoted by Willebrand)⁸ who found no change in specific gravity or hemoglobin content after 10 minutes of hard exercise, and of Mitchell⁹ who obtained inconstant increase and one not proportionate to the rise in red corpuscles. On the other hand, Boothby and Berry,¹⁰ Schneider and Havens¹¹ and Brown¹² calculated increases of 8.3 per cent, 3.5 per cent to 10.9 per cent,

and 8.5 per cent respectively. Orias,¹³ working with somewhat different conditions, concluded that there was a real drop in the hemoglobin in his subjects after 15 days of intense exercise and a gradual return to a normal content in the blood within a period of 4 to 6 days following the cessation of exertion. Since the length of activity was so great he was probably justified in explaining this decrease as due to red cell destruction. A similar conclusion was reached by Broun¹⁴ upon study of the blood picture of dogs after they had been subjected to prolonged periods of activity.

Although the total hemoglobin content did not change significantly in these studies, there was a real decrease in the amount of hemoglobin in the cells after exercise (2.75 ± 0.28 micromicrograms; Chart I, Table 1). These data lend weight to the suggestion of Mitchell⁹ that incoming cells with less hemoglobin value than normally found in the peripheral circulation accounted for the disproportionate and highly variable response of the hemoglobin content. Accompanying this decrease in corpuscular hemoglobin there was no real alteration in the amount of hemoglobin in each cell in proportion to its volume. The difference in the average corpuscular concentration in 40 experiments before and after exercise was found to be less than its probable error (Table 1).

The volume percentage as determined by the hematocrit method with a small amount of blood showed no significant change which could be attributed to the effects of exercise (Table 1). With the real increase in the number of cells (average 550,000) there was only a slight increase in the total volume (0.09 ± 0.04 per cent). However, with the same method of volume determination, Smith and Prest⁶ found that women with total counts of 420,000 cells less than the normal average also had about 4 per cent lower total volumes. If a proportional increase in volume had accompanied the rise in the number of cells in these experiments, it should have been of sufficient magnitude to have been measured by the method employed.

In contrast to these findings are those obtained by previous investigators. Edgecombe¹⁵ showed that with a fall in amount of hemoglobin was a rise in the percentage volume of erythrocytes. The latter was augmented considerably when profuse perspiration occurred. Broun,¹² Scheunert and Müller,¹⁶ Scheunert and Krzywanek,^{17a, 17b, 18} Krzywanek and Arnold,¹⁹ and Arnold and Krzywanek²⁰ obtained real increases in volume percentage. Arnold and Krzywanek furthermore noted that the increase in volume was not as great in man as in experimental animals.

Though the volume percentage did not change, the decrease in the average corpuscular volume after exercise was found to be real (7.85 ± 0.99 cubic micra; Chart I, Table 1). Price-Jones^{21,22} has emphasized the increase in cellular diameter following vigorous exercise (running up and down 6 flights of stairs 3 times). He

associated the increase with a diminution in alkalinity of the blood. Wiechmann and Schurmeyer²³ verified these observations on cells during muscular fatigue. Broun¹² stated that his data were too few to give figures on the average cell size, but he believed they tended to confirm the work of Price-Jones. On the other hand, Scheunert and Krzywanek^{17a, 17b} stated that the volume of a single cell remained constant during rest and activity. Dryerre, *et al.*,²⁴ found no real difference between the mean diameters of erythrocytes before and after violent exercise, although from their tables the average for the readings taken after exercise was slightly less than the one before. Ponder and Saslow²⁵ reported that they obtained no evidence of an increase in diameter of the average corpuscle after exercise (running down 6 flights of stairs and back again) that could not be accounted for by the error of the method. When their determinations for 25 persons at rest and after exercise were averaged, the mean for those after exercise was $0.04\ \mu$ less than the one before.

In order to test the decrease in cell volume in this series of experiments as found by the division of the total volume by the total cell count, 5 sets of slides were made for the measurement of cells from dried films. Cells magnified 1300 times were projected by means of the euscope and measured directly with very fine compasses on a transparent protractor divided into $\frac{1}{2}$ mm. parts (method of Sauder and Toomey).²⁶ The ground glass screen was lighted evenly so that almost all the cells could be measured (2 diameters for each of 200 cells on 5 slides before exercise and 5 slides after exercise). The results were as follows:

TABLE 3.—EFFECT OF EXERCISE ON DIAMETER OF RED CELLS.

		Before exercise, micra.	After exercise, micra.
1	(Average 400 diameters, 200 cells)	7.94	7.78
2	" " "	7.92	7.88
3	" " "	7.67	7.69
4	" " "	7.64	7.68
5	" " "	7.60	7.65
Average (from 2000 diameters, 1000 cells)		7.78	7.76

The difference ($0.02\ \mu$) between the two means was found to be about equal to its probable error and therefore not significant. These data confirmed those of Dryerre, *et al.*,²⁴ and Ponder and Saslow²⁵ in that the variation came within the limit of error of the method and could not be proved real. The measurement of dried cells is admittedly inaccurate, but even so the tendency was toward cells of less diameter, when all data were averaged, rather than greater, as indicated by Price-Jones. If, as Haden²⁷ noted, a change in diameter of $1\ \mu$ caused a variation of 44 per cent in cell volume, then a difference of about 9 per cent in volume as found in these studies might well be difficult to detect in dried cells.

Six possible causes for the increase in the number of erythrocytes have been outlined by Hawk:²⁸ (1) production of new cells; (2) concentration of blood through increased urine formation and copious perspiration; (3) concentration of blood through vasomotor contraction and rise in blood pressure; (4) concentration of the blood through evaporation in the lungs; (5) sudden passage into the circulating blood of a large number of cells lying in various parts of the body and inactive before the time of muscular exercise; (6) passage of fluid from the blood to the active muscles. Long continued exercise may produce effects depending on these and other factors, but the initial increase in corpuscles in the peripheral blood immediately after 2-minute periods of hard exercise as described in these studies would seem to be due largely to a sudden shower of cells from reservoirs, principally the spleen, in other parts of the body, Mitchell,⁹ Edgcombe,¹⁵ Hawk,²⁸ Broun,¹² Scheunert and Müller,¹⁶ Scheunert and Krzywanek,^{17a, 17b, 18} Abderhalden and Roske,²⁹ Barcroft and Poole,³⁰ Barcroft and Stevens.³¹ No perspiration was noted in the present experiments except in the 5 series where only the dried smears were made for the measurement of cells. There was also no definite change in the number of reticulocytes. The rapidity of the response of the erythrocytes after short periods of vigorous exercise, the lack of sensible perspiration, and the failure to demonstrate an increase in new cells would be indirect evidence in confirmation of the statement of Barcroft and Poole³⁰ that "there seems to be no doubt, however, that the spleen does play a considerable rôle in the increment of corpuscles during asphyxia and during exercise, even though it may not be responsible for the whole phenomenon."

Conclusions. 1. Two-minute periods of strenuous exercise produced a transient increase in the total number of red corpuscles per cubic millimeter in the peripheral blood stream.

2. This short but severe exertion failed to alter significantly the total amount of hemoglobin or the volume percentage of erythrocytes.

3. A drop occurred in the estimated mean corpuscular volume and mean corpuscular hemoglobin immediately after exercise, suggesting that cells were present smaller in size and containing less hemoglobin than those normally circulating in the capillary beds of the body surface.

4. The smaller amount of hemoglobin was correlated with the decreased volume of the corpuscles, so that the proportion of hemoglobin to other corpuscular contents remained relatively constant during rest and exercise.

BIBLIOGRAPHY.

1. Wintrobe, M. M.: *The Erythrocyte in Man*, Med., 1930, 9, 195.
2. Van Allen, C. M.: *An Hematocrit Method*, J. Lab. and Clin. Med., 1924-1925, 10, 1027.

3. Van Allen, C. M.: An Hematocrit Method, *J. Am. Med. Assn.*, 1925, 84, 202.
4. Wintrobe, M. M.: The Volume and Hemoglobin Content of the Red Blood Corpuscles, *Am. J. Med. Sci.*, 1929, 177, 513.
5. Smith, C.: Normal Variations in Erythrocyte and Hemoglobin Values in Women, *Arch. Int. Med.*, 1931, 47, 206.
6. Smith, C., and Prest, M.: Further Observations on the Erythrocyte Values in Women (to be published).
7. Gavett, G. I.: A First Course in Statistical Method, New York, McGraw-Hill, 1925, p. 183.
8. Willebrand, E. A.: Ueber Blutveränderungen durch Muskelarbeit, *Skan. Arch. f. Physiol.*, 1903, 14, 176.
9. Mitchell, J. K.: The Effect of Massage on the Number and Hemoglobin Value of Red Blood Cells, *Am. J. Med. Sci.*, 1894, 107, 503.
10. Boothby, W. M., and Berry, F. B.: The Effect of Work on the Percentage of Hemoglobin and Number of Red Corpuscles in the Blood, *Am. J. Physiol.*, 1915, 37, 378.
11. Schneider, E. C., and Havens, L. C.: Changes in the Blood After Muscular Activity and During Training, *Am. J. Physiol.*, 1915, 36, 239.
12. Broun, G. O.: Blood Destruction During Exercise. I. Blood Changes Occurring in the Course of a Single Day of Exercise, *J. Exp. Med.*, 1922, 36, 481.
13. Orias, O.: Teneur du sang en hémoglobine chez l'homme en Argentine. Facteurs qui l'influencent, *Compt. rend. Soc. biol.*, 1930, 15, 711.
14. Broun, G. O.: Blood Destruction During Exercise. II. Demonstration of Blood Destruction in Animals Exercised After Prolonged Confinement, *J. Exp. Med.*, 1923, 37, 113.
15. Edgecombe, W.: The Effect of Exercise on the Hemoglobin With Reference to the Value of Rest in the Treatment of Anemia, *British Med. J.*, 1898, 1, 1650.
16. Scheunert, A., and Müller, C.: Einfluss von Bewegung und sportlicher Höchstleistung auf die Blutbeschaffenheit des Pferdes, *Arch. f. d. ges. Physiol.*, 1926, 212, 468.
- 17a. Scheunert, A., and Krzywanek, W.: Über reflectorisch gergelte Schwankungen der Blutkörperchenmenge, *Arch. f. d. ges. Physiol.*, 1926, 212, 477.
- 17b. Scheunert, A., and Krzywanek, W.: Weitere Untersuchungen über Schwankungen der Blutkörperchenmenge, *Arch. f. d. ges. Physiol.*, 1926, 213, 198.
18. Scheunert, A., and Krzywanek, W.: Über die Beziehungen der Milz zu den Schwankungen der Menge der roten Blutkörperchen, *Arch. f. d. ges. Physiol.*, 1926-1927, 215, 187.
19. Krzywanek, W., and Arnold, A.: Der Anteil der roten Blutkörperchen im menschlichen Blut bei Ruhe und Bewegung, *Arch. f. d. ges. Physiol.*, 1927, 216, 640.
20. Arnold, A., and Krzywanek, W.: Ein weiterer Beitrag zur der Frage der Erythrocytenvermehrung im menschlichen Blut nach körperlicher Arbeit, *Arch. f. d. ges. Physiol.*, 1928, 220, 361.
21. Price-Jones, C.: The Diurnal Variation in the Sizes of Red Blood Cells, *J. Path. and Bact.*, 1920, 23, 371.
22. Price-Jones, C.: Individuality in the Size of Red Cells, *J. Path. and Bact.*, 1930, 33, 1173.
23. Wiechmann, E., and Schurmeyer, A.: Untersuchungen über den Durchmesser des roten Blutkörperchen, *Deutsch. Arch. f. klin. Med.*, 1925, 146, 362.
24. Dryerre, H., Millar, W. G., and Ponder, E.: An Investigation into the Size of Human Erythrocytes Before and After Exercise, *Quart. J. Exp. Physiol.*, 1926-1927, 16, 69.
25. Ponder, E., and Saslow, G.: The Measurement of Diameter of Erythrocytes. The Diurnal Variation and Effect of Exercise, *Quart. J. Exp. Physiol.*, 1930, 20, 41.
26. Sauder, H. R., and Toomey, J. A.: Rapid Measurement of Red Cells, *Am. J. Dis. Child.*, 1931, 41, 823.
27. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, *Am. J. Med. Sci.*, 1931, 181, 597.
28. Hawk, P. B.: On the Morphological Changes in the Blood After Muscular Exercise, *Am. J. Physiol.*, 1904, 10, 384.
29. Abderhalden, E., and Roske, G.: Die Bedeutung der Milz für Blutmenge und Blutzusammensetzung, *Arch. f. d. ges. Physiol.*, 1927, 216, 308.
30. Barcroft, J., and Poole, L. T.: The Blood in the Spleen Pulp, *J. Physiol.*, 1927-1928, 64, 23.
31. Barcroft, J., and Stevens, J. G.: Observations Upon the Size of the Spleen, *J. Physiol.*, 1927-1928, 64, 1.

CONTACT DERMATITIS (VENENATA).

DISTRIBUTION AND IMPORTANCE OF THE HELENIUMS AS A CAUSE OF CONTACT DERMATITIS IN THE UNITED STATES.

BY RAY M. BALYEAT, M.A., M.D., F.A.C.P.,

ASSOCIATE PROFESSOR OF MEDICINE AND LECTURER ON DISEASES DUE TO ALLERGY,
UNIVERSITY OF OKLAHOMA MEDICAL SCHOOL,

HERBERT J. RINKEL, B.S., M.D.,

AND

T. R. STEMEN, M.A.,

INSTRUCTOR, BIOLOGY DEPARTMENT, CENTRAL HIGH SCHOOL,
OKLAHOMA CITY, OKLA.

DURING the past two years we have found *Helenium microcephalum* D.C. to be a rather common cause of contact dermatitis (venenata). Weber¹ names *Helenium autumnale* in his list of cutaneous irritants. Andrews² states that the heleniums (the sneeze weed family) belong to the group of plants which are known to cause systemic reaction following contact. We have found no other reference concerning the helenium family in medical literature. Since we have seen a number of cases of severe dermatitis due to the heleniums, and knowing that the plant is very abundant in the Southwest, we are led to believe that the helenium family may be of considerable importance in the cause of dermatitis through many sections of this country, which accounts for our detailed study of the distribution of this plant throughout the entire United States.

Distribution. The finding of a number of severe cases of dermatitis venenata due to the heleniums caused us to investigate every section of our state, as well as New Mexico, Texas, Kansas and Arkansas, from the standpoint of the abundance of the helenium plant. We found the plant very abundant along the roadsides and in the poorly drained areas of the prairies of the panhandle of Texas and of many sections of New Mexico, western Kansas and western Oklahoma. Occasionally plants were found in eastern Oklahoma and western Arkansas.

Questionnaires were sent to the professors of botany of the universities and agricultural colleges in every state in the Union. A detailed reply from all but 6 states was obtained. Information concerning the plant in these states was obtained from the foresters.

Information received from the professor of botany, University of Kansas, stated that the plant is fairly commonly found in the eastern section of the state. The professor of botany, University of Arkansas, reported the plant rather generally distributed but nowhere very abundant in the state. From Louisiana a report came that it is very abundant along the roadsides and waste places.

Nevada, Arizona, Idaho, California and Utah all report one or more species of *helenium* to be moderately common and fairly well distributed throughout their states. We were interested in the reports which came from Oregon and Washington. The professor of botany of the University of Oregon stated that "hundreds of acres of the *Helenium autumnale* grow along the Columbia River, less elsewhere." He reports a number of other varieties in the state. Likewise information from the professor of botany of the University of Washington is similar in character. Wyoming reports show that the plant is fairly abundant along the Platte River. In Colorado it occurs but rarely. In Montana, North and South Dakotas and Nebraska information was given us that it is common in low places and fairly well distributed throughout these states. In Minnesota the plant is abundant as far north as the Twin Cities. In Wisconsin it occurs but rarely.

Information received shows the plant to be quite well distributed and in some places very abundant in Ohio, Indiana and Illinois. Charles C. Deam, Research Forester for the State of Indiana, states as follows:

"*Helenium autumnale* is a common plant in all parts of Indiana. . . . It is a denizen of low ground and is most frequently found in low open fields in wet land and along ditches. It rarely grows in thick colonies and is usually found as single plants here and there, but sometimes it grows fairly thick. On the contrary, *Helenium nudiflorum* is usually a common plant where it is found and grows in large colonies. I have seen it by acres, usually in waste land or pasture fields. All species of the genus are avoided by stock and are reputed to be poisonous to them. . . . This month (October, 1931) I found a pasture of about 3 acres of *Helenium tenuifolium*. . . . The species was almost a pure stand and stock did not touch it."

A report from the Virginia Polytechnic Institute shows that the plant is quite widespread in Virginia along the Blue Ridge and Allegheny Mountains. The professor of botany at Charlottesville, Va., reported it to be fairly common, but rather abundant along the southwestern mountains of the state, and said that it was found in fair abundance around Richmond. From our reports we find it fairly common along the streams in New York and moderately abundant in Maryland, Delaware and New Jersey. The professor of botany at the Massachusetts Agricultural College at Amherst advises us that the plant is common in Berkshire County but rare in other sections of the state. It is found in Connecticut, Rhode Island and Maine but not abundant in these three states.

All states south of the Ohio River and east of the Mississippi, except Florida, reported one or more species of the *heleniums* to be common and fairly widely distributed. It rarely occurs in Florida.

A great many botanists reported that *Helenium autumnale* was common. After studying the *helenium* family in detail during the

last few months, and after a conference with the Assistant Director of the New York Botanical Garden, Marshall A. Howe,³ we feel that many of the botanists in reporting *Helenium autumnale* were possibly referring to some other species, as there are many species.

DISTRIBUTION OF THE HELENIUMS IN THE UNITED STATES

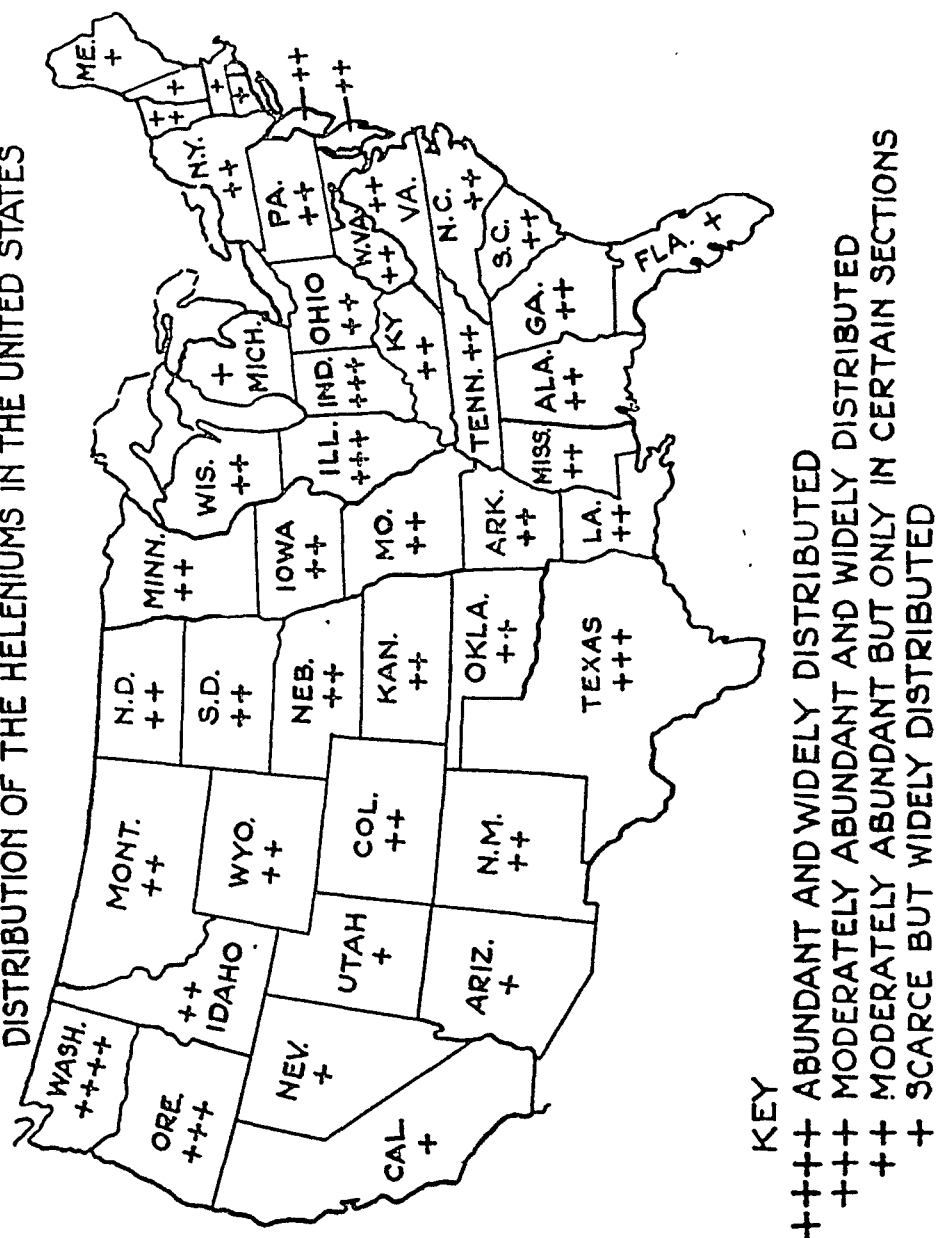


FIG. 1.—Map showing distribution of the heleniums in the United States. More than 50 per cent of the states show the plant to be fairly abundant and widely distributed.

Helenium autumnale is very common in the eastern third of the United States. In the midcentral territory *Helenium microcephalum* D. C. is common. In the western section of our country *Helenium montanum* and *Helenium nudiflorum* are more common and the *autumnale*, if found, is rare. From a practical standpoint it makes no difference which species was found, since the characteristic of the genus is an oleoresin, which is the part of the plant that produces the dermatitis.

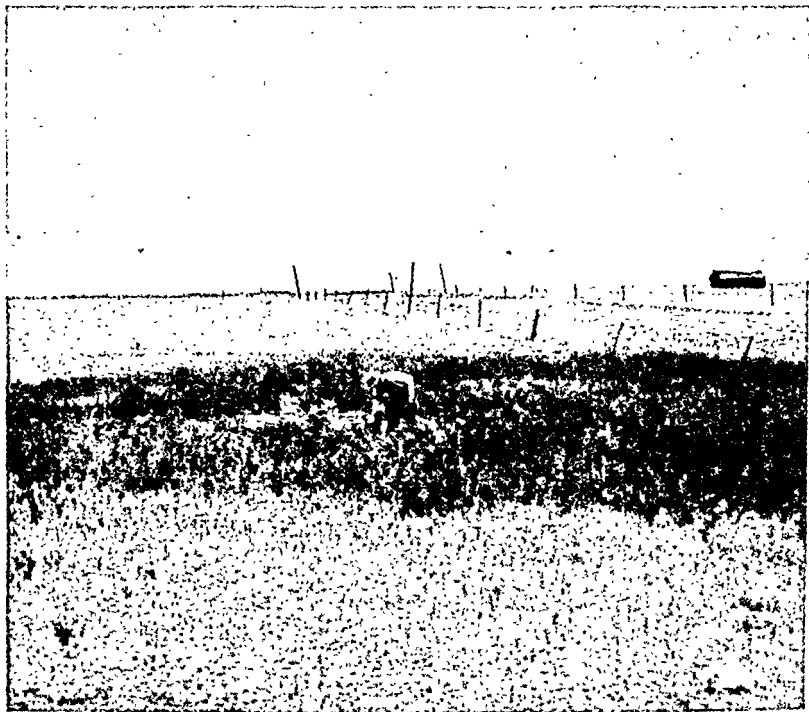


FIG. 2.—A patch of *Helenium microcephalum* D. C. (sneeze weed) on the plains of western Texas.

The Botany of the Heleniums.⁴ The heleniums are annual, biennial or perennial herbs. The leaves are alternate, entire or toothed, often prolonged downward on the stem. Heads mostly with rays and peduncled. The involucre is broad and short, the bracts in one or two series and spreading or bent backward abruptly. Receptacle convex, oblong or subglobose, naked. The ray flowers are pistillate and fertile, or neutral, the rays wedge-shaped, 3 to 5 toothed. The disk flowers perfect, fruit-producing, corollas yellow, purple or brown, their teeth glandular-pubescent. The anthers are 2-toothed or arrow-shaped at the base; stigmas of the disk flattened and truncate; achenes broadened upward, ribbed; pappus of 5 to 8 awn-tipped scales.

An outstanding character of the genus is the presence of bitter, aromatic, resinous globules on the leaves, stems and flowers. When collecting the plant the resin adheres readily to the hands. Under the hand lens the resin

appears as minute globules of oil, very thickly distributed over the surface of the plant.

Helenium Autumnale. A perennial with a more or less pubescent stem, narrowly winged by the decurrent bases of the leaves, 2 to 6 feet high. Leaves are oblong, lanceolate or ovate-lanceolate, 2 to 5 inches long, $\frac{1}{4}$ to 2 inches wide, prominently toothed, sessile (attached to stem without stalk). Heads are numerous, borne on stalks of great length, 1 to 2 inches broad, including rays; rays, 10 to 18, drooping, bright yellow; disks spherical.

The stem, leaves and flowers are sprinkled with bitter aromatic resinous globules.

This species is known to hybridize with *Helenium nudiflorum*. Many of the specimens collected show evidence of this hybridization.

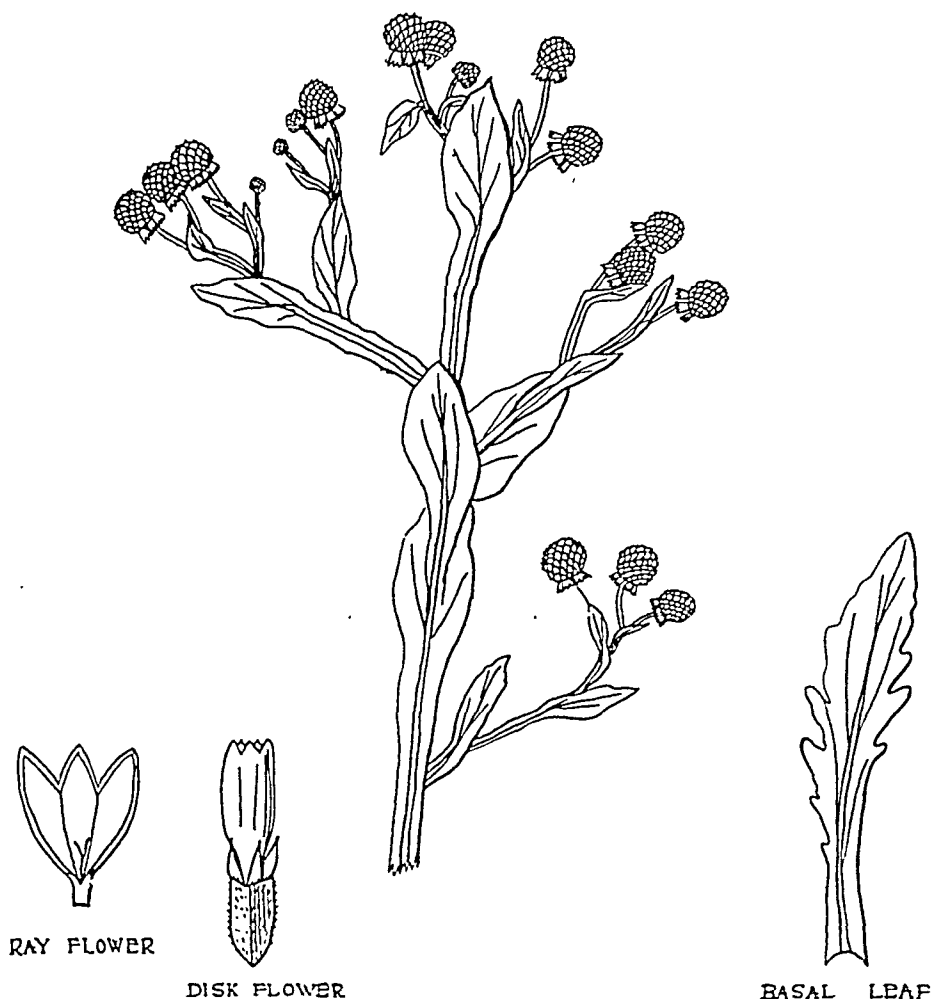


FIG. 3.—Drawing showing the botany of *Helenium microcephalum* D. C.

This species grows in low, usually poorly drained prairies and meadows; blooms from July to October. It is widely distributed from Quebec to Florida, Manitoba, Oregon, Oklahoma, Texas and Arizona.

Helenium Microcephalum D. C. *Helenium microcephalum* D. C. (sneeze weed or bitterweed) is an annual leafy plant, 1 to 2½ feet high, with winged angular stems. The leaves are simple, the blades oblong to lanceolate, 3 to 8 cm. long, clasping the stem and continuing down the stem fully half

the length of the blade, those of the lower leaves often toothed. Flowers are 5 to 6 mm. in diameter, disk globular, the rays 3 to 5 mm. long, yellow, wedge-shaped, folded against the stems.

The plant grows in moist soil, depressions that are locally called hog-wallows, and banks of small streams.

It is found growing in southern Oklahoma, Texas and adjacent Mexico.

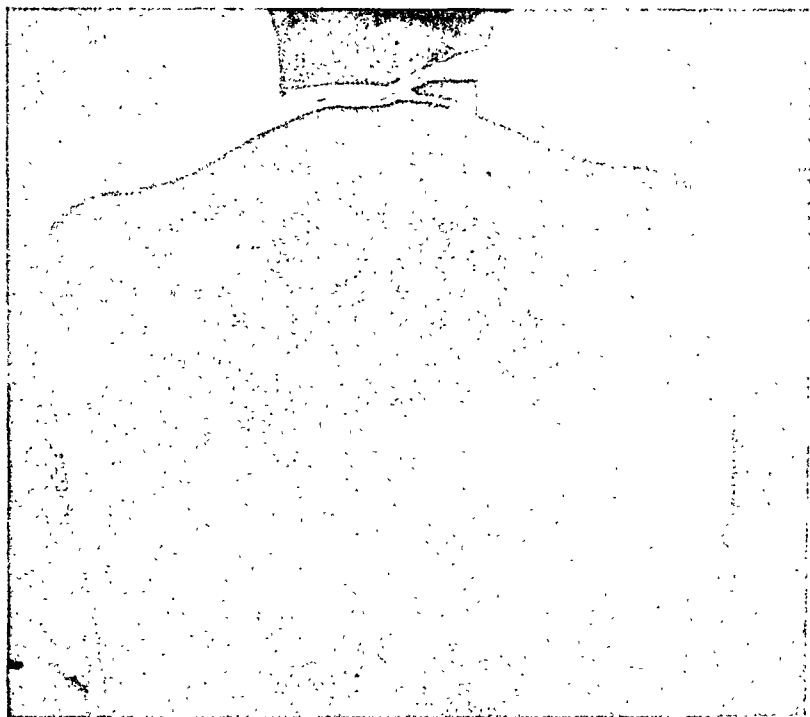


FIG. 4.—Results of patch test 24 hours after application of ground leaves of *Helenium microcephalum* D. C.

We are indebted to Dr. Mark R. Everett, professor of biochemistry and pharmacology at the University of Oklahoma Medical School, for a preliminary report upon the nature of the active substance. He states that the irritant is secreted upon the surfaces of the leaves and flowers in the form of a resin. The active substance is nonvolatile, is entirely extracted by absolute ethyl alcohol at room temperature, is also soluble in benzene or ether, but relatively insoluble in petroleum ether or water. Further chemical studies on the exact nature of the irritant are being made by Dr. Everett.

Skin Test Findings. Patch tests were run with the ground-up leaves, flowering tops, the oleoresin as a whole, and the various fractions. We were very much interested in the fact that of all the substances we have ever used in patch testing the oleoresinous

material from the helenium plant produced the most marked local and systemic symptoms. A 10 per cent solution of the oleoresinous material in olive oil was used in doing the patch tests. The absolute ethyl alcohol fraction gave by far the most marked reactions. Some patients would obtain not only a marked local reaction in the course of a few hours, but would also have systemic reactions manifested by abdominal cramps, with diarrhea. We mention this to show the marked toxicity of the resinous material. Patients should be carefully watched following testing, as we have found systemic reactions not uncommon. For patch testing a 10 per cent solution of the ground-up leaves or heads, or the extracted oleoresin in olive oil, may be used. (Careful) controls on nonsensitive patients should always be made.

Importance of the Heleniums as a Cause of Contact Dermatitis. During the past 2 years we have seen several cases of contact dermatitis due to *Helenium microcephalum* D. C. Two of these cases have been recently reported in detail by one of us.⁵ As we review a number of cases of dermatitis of unknown origin whom we saw before we were testing with the oleoresin of helenium, we feel confident that a number of them were due to contact with this plant. Since in our clinic we deal only with the allergic phase of dermatology, the number of cases of contact dermatitis who come to us would naturally be comparatively small compared with those who apply to the dermatologist for relief of their symptoms. We feel, therefore, since we have seen a number of cases during the last 2 years the cause of which we could trace to one of the heleniums, that evidently the dermatologists in the Southwest have also seen a large number of similar cases. We find on personal interview with some of the leading dermatologists in this section that they are entirely unfamiliar with the plant. We find in careful review of the medical literature during the past 10 years that the plant is mentioned only twice as a possible cause of dermatitis, but we can find no record of a report of a single case of contact dermatitis, the cause of which has been proven to be contact with helenium. We would naturally conclude that many cases of contact dermatitis due to helenium are being unrecognized by the dermatologist and the allergist.

In our reports from the botanists from various states of this country we find that in about 50 per cent of the states the plant is profuse and widely distributed; in about 35 per cent it is fairly abundant and widely distributed, but it occurs in all the states. The habitat of the plant is the roadside, especially at the side of the ditch along the road. It occurs in the poorly drained areas of the semi-arid sections of the United States. Frequently the plants are individual and do not grow close together. We have observed them around barn lots and in the wheat fields as individual plants, but many places where there is a wet area there will be from a quarter

acre to several acres of the plant growing very thickly. Some of the varieties of helenium are described in various garden books and are used as borders on the lawn. The possibility of contact with the plant is (fairly) great; for example, those who work on the public roads, the farmer, the telegraph and telephone lineman, the man who works in the wheat field, the rancher, the hunter, the oil-field worker and in some cases the women who work with their shrubbery, certainly have adequate contact with the plant. Coca⁶ states that, differing from the usual allergic individual who is subject to the atopic hereditary influence, about 70 per cent of the white race may have contact dermatitis. In other words, nearly three-fourths of those who have adequate contact with the heleniums have an excellent opportunity to develop a dermatitis.

As previously stated, there are many varieties of the helenium. In some sections of the country *Helenium autumnale* grows, while in other sections *Helenium microcephalum* D. C., etc., but since the oleoresin is the characteristic of the genus we are not primarily concerned with the individual species. Since one of the species of the helenium grows in every state in the Union, and in the majority of the states is widely distributed and fairly abundant, the number of people who come in intimate contact with the plant is evidently very large. Since about 70 per cent of those who come in contact have a possibility of developing a dermatitis, surely this plant is an important factor in the United States in the cause of contact dermatitis. It seems that it is frequently overlooked as an etiologic factor.

The cases of dermatitis due to helenium we have seen have all come from Oklahoma, New Mexico, Texas and Kansas, and our personal observation of the plant has been in these states. Knowing what we do about the abundance of this plant in these states, and realizing the severity of its toxicity, we naturally became very much interested in the plant and feel that we are justified in making a detailed report.

Summary. 1. Very little concerning the helenium family can be found in medical literature.

2. *Helenium microcephalum* D. C. is an important etiologic factor in contact dermatitis (venenata) in the Southwest.

3. One or more species of the helenium family grow in every state in the Union.

4. The irritating substance is an oleoresin. It is soluble in absolute alcohol, benzene or ether and relatively insoluble in water.

5. Since the characteristic of the genus is an oleoresin, any species should be important from the standpoint of contact dermatitis.

6. Patch tests should be made with great care because a systemic reaction may occur, manifesting itself by abdominal cramps, diarrhea, conjunctivitis and headache.

7. The widespread distribution of the heleniums and their habitat affords adequate contact for the development of a specific sensitization.

REFERENCES.

1. Weber, L. F.: A List of Cutaneous Irritants, Arch. Dermat. and Syph., 1930, 21, 761.
2. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1930.
3. Personal communication.
4. Britton, N. L., and Brown, H. A.: Illustrated Flora of the Northern United States, Canada, and British Possessions, New York, Charles Scribners' Sons, 1913. Small, J. K.: Flora of the Southeastern United States, 2d ed., New York, published by the author, press of New Era Printing Company, Lancaster, Pa., 1913. Gray, A.: Gray's New Manual of Botany, 7th ed., New York, Cincinnati and Chicago, American Book Company, 1908.
5. Rinkel, H. J.: Contact Dermatitis and Eczema: With Report of Nine Cases, read before the Southern Medical Association, Section on Dermatology and Syphilology, New Orleans, November 19, 1931, unpublished.
6. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Baltimore, Charles C Thomas, 1931.

THE RELATION OF NEOCINCHOPHEN TO THE QUESTION OF
CINCHOPHEN TOXICITY.*

By JOHN STAIGE DAVIS, JR., M.D.,

RESEARCH ASSISTANT IN SURGERY, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK.

(From the Department of Surgical Research, Cornell University Medical School.)

PHENYLCINCHONINIC acid (cinchophen) was discovered in 1887 by Doebner and Gieseke.¹ In 1908 Nicolaier and Dohrn² described its therapeutic action, and since that time it has been extensively used as a therapeutic agent. In 1913 Phillips³ described idiosyncratic skin reactions to cinchophen; and in 1922 Schroeder⁴ called attention to the toxic action of cinchophen. In 1923 Worster-Drought⁵ reported a case developing urticaria and jaundice after the use of cinchophen. Since that time clinicians have become increasingly more cautious in the use not only of this drug but also of its derivatives, the most important of which is neocinchophen.

In 1929 Reichle⁶ collected and reported 49 cases of toxic cirrhosis of the liver due to cinchophen or its derivatives. Ten of these patients died. In these cases the dose necessary to produce symptoms varied from 15 grains to 4000 grains administered over various periods. In 1930 Rabinowitz⁷ collected 50 cases, 25 of which died and autopsies were performed on 20. During the discussion of his paper 6 more cases were reported, 5 of which died. It is interesting

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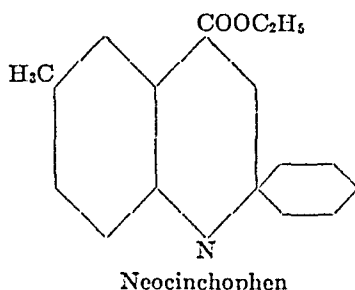
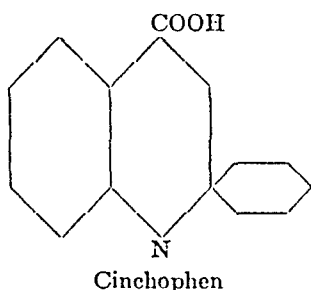
that none of the deaths were due to neocinchophen alone. In 1925 Cabot⁸ reported a case of acute yellow atrophy said to be due to a course of "Weldona," a proprietary preparation which was supposed to contain a carbonate, cascara sagrada and neocinchophen. Grolnick⁹ also reported a case of toxic hepatitis due to "Weldona," symptoms having developed after 12 tablets were taken, with recovery of the patient. There is, however, considerable doubt as to the contents of "Weldona." In 1924 the American Medical Association published the results of its analysis of these large lavender tablets which were found to contain sodium salicylate and an unidentified vegetable extract. No alkaloids, iodids, acetylsalicylic acid, phenyl salicylate, or neocinchophen were found. Similarly the Health Bureau of Rochester, N. Y. made tests on "Weldona" in 1925. In 1926 the Chemical Laboratory of the American Medical Association completed another analysis of "Weldona" with the same result. Accordingly the *Journal of the American Medical Association* concluded,¹⁰ "It seems evident from these various analyses, made over a period of years, that 'Weldona,' like so many other patent medicines, is a name rather than a thing—while the name has remained constant the composition has varied." Walker¹¹ has reported 2 cases of toxic hepatitis, both of which died.

Parsons and Harding added 4 more fatal cases.¹² In a survey issued by the Calco Chemical Company¹³ in October, 1931, 100 cases of suspected poisoning from phenylcinchoninic acid or its derivatives throughout the world since 1913 were reported. Of these 36 died, a large proportion of which were proven to be acute yellow atrophy at autopsy. Based upon these late and rather complete figures, however, a rough computation of the incidence of fatal intoxication is about 1 to 500,000 patients for this country. In May, 1931, Ross¹⁴ reported 5 cases of acute hepatitis, 3 of which died and gave proof of the diagnosis at autopsy. One of these had taken tolysin intermittently for a period of 2 months, exact dose unknown. Prior to this there had appeared in the literature no authentic occurrence of a fatality due to neocinchophen. This case has been investigated but, because of the difficulty of obtaining complete facts at a labor camp in Canada where the administration occurred, the question of substitution cannot be settled definitely. The patient claimed to have purchased tolysin for self-medication but at the time of medical attendance none of the drug could be found to ascertain whether substitution had taken place. In July, 1931, Sherwood and Sherwood¹⁵ reported a case of acute hepatitis due to cinchophen with recovery.

The wide interest aroused in the medical profession by the cited publications led the author to the further studies reported herewith. Although various observers have occasionally noted the lesser toxicity of neocinchophen, it appeared to the author that the degree of difference in toxicity has neither been sufficiently studied nor

adequately described. Louise Rotter¹⁶ was the first to show the profound pharmacologic differences engendered by transposition or multiplication of side-chains upon the quinolin nucleus. Briefly summarized, it is impossible to predict toxicity from the apparent similarity of structural formulæ. These differences in toxicity have been attributed to various factors. Neocinchophen has been thought to be absorbed more slowly and to be less irritating to the kidneys. Hanzlik reported¹⁷ 10 years ago that cinchophen sometimes produced albuminuria and a diminished phthalein output. Furth and Kuh,¹⁸ however, state that tolysin is absorbed as completely as is cinchophen but somewhat more slowly. They performed most extensive experiments upon rabbits, dogs and humans, and from their work reached a conclusion which alters the older theories of physiologic chemistry, namely, that tolysin is absorbed by the intestinal mucosa without first undergoing any saponification. On the contrary, Hanzlik¹⁹ in 1926 had postulated that the advantage of neocinchophen over the salicylates and cinchophen (relative absence of side-actions) was secured at the expense of poor solubility and absorbability of the neocinchophen. He concluded that therefore greater doses of neocinchophen must be taken to be effective, and that its apparent therapeutic advantage thus becomes less and the economic disadvantage to the patient becomes greater.

The respective structural formulæ of cinchophen and neocinchophen are shown below, and it will be noted that whereas cinchophen is an acid, neocinchophen is an organic *ester*, not of *cinchophen*, but of paramethylphenylcinchoninic acid.



Once absorbed, the actions of these drugs have been assumed to be similar. The earliest and most important action noted was to increase the urinary output of uric acid. Probably this has occasioned more discussion than any other chemical subject in medicine. It is needless to enter into the controversy here, since it has not been disputed that this effect, whatever its cause, does occur. Subsequent to such clinical demonstrations it was discovered that these drugs were excellent antipyretics and analgesics and seemed to exert a semispecific action, so far as pain and disability were concerned, upon acute and chronic inflammatory processes of the bones, joints and tendons. Contemporaneously with the clinical studies,

pharmacologists in Germany were not idle in the wider investigation of these chemicals. Mendel²⁰ demonstrated paralysis of the ameboid movements of the leukocytes, followed by complete disintegration of their nuclei after the injection of sodium atophan into the thoracic lymph sac. From these results he assumed that the increase in uric acid elimination was due to leukocytic destruction *in vivo*, with the consequent release of large amounts of nucleoprotein into the blood stream. Starkenstein²¹ later attempted to refute the conclusion of Mendel by stating, "The paralyzing action of atophan on the leukocytes explains, it is true, the depressing effect of this substance on inflammation, but the effect of atophan on purin metabolism is not an action on metabolism but an influence upon uric acid excretion." This view is generally accepted today. Dohrn²² claimed that a slight leukocytosis followed the ingestion of atophan during the ensuing 4 or 5 hours and subsided within 24 hours. From these data he believed that leukocytic destruction played no part in the increase in uric acid elimination. We have been unable to obtain any increase in leukocytes after the ingestion of 30 grains of neocinchophen. It is a generally accepted hypothesis that this group of drugs increases renal permeability to uric acid, and Graham²³ believes that cinchophen at least facilitates the transport of uric acid to the blood from the tissue fluids and sodium biurate deposits. Griesbach²⁴ suggests that cinchophen tends to check the storage of uric acid in the tissues; and according to Starkenstein²⁵ it may inhibit purin metabolism.

Any attempt to review the entire literature on the value of neocinchophen is beyond the scope of this paper. Suffice it to say that Pulay²⁶ found it valuable in cases of urticaria; Bendix²⁷ used it in rheumatic fever; Jokl²⁸ used it in polyarthritis; Chace, Myers and Killian²⁹ found it the drug of choice in cases of suspected renal irritation; and many others similarly employed this ester. Barbour, Lozinsky and Clements³⁰ in 1923 reported 41 patients whom they had treated with varying amounts of tolysin. They concluded that tolysin appeared to be a very safe drug and could be administered more continuously than salicylates and in larger doses. Two of their patients received 450 grains within 8 days without any untoward symptoms. Boots and Miller³¹ treated 20 rheumatic fever patients with tolysin. They compared these effects with those of sodium salicylate. In only 1 case did neocinchophen seem more toxic to the kidneys than sodium salicylate. The study seemed to show, however, that symptoms and signs of toxicity similar in character to those of salicylism occurred with full therapeutic doses of neocinchophen. Five of the 20 patients were free from symptoms of toxicity such as nausea, renal irritation, vomiting, or urticaria. They concluded that the symptoms of toxicity were not so marked in neocinchophen as in the case of the salicylates. Poynton,³² in Great Britain, was favorably impressed with this ester.

The literature is replete with writers' impressions that their patients did not always tolerate cinchophen well. Chace and Fine³³ 17 years ago noticed that their patients were upset by it and that it could be taken only when well diluted with water or in conjunction with bicarbonate of soda. Occasionally patients have been seen who have an idiosyncrasy to the drug such that a very small dose will produce toxic symptoms. Evans and Spence³⁴ in Great Britain collected 3 cases, 1 of which had a family history of idiosyncrasy to the drug. In one instance cinchophen would produce an attack of gout.

It has been noticed that certain individuals react in an abnormal manner either to derivatives of the quinolin nucleus or to other derivatives of coal tar. Accordingly many clinicians in administering these drugs have deemed it wise to give small initial doses for the purpose of testing the patient's tolerance to the drug employed. Rabinowitz,⁷ however, says that these precautions even when coupled with intermittent dosage often do no good. He contends that certain individuals are predisposed to hepatitis, particularly those with gall bladder disease, hepatic cirrhosis, chronic alcoholism, chronic nephritis, etc. Those who have in the past suffered from liver diseases associated with jaundice; those who have had eclamptic difficulty with pregnancy; and those showing other evidences of cinchophen intolerance, are apparently especially so predisposed. The drug appears particularly dangerous in states of hepatic damage accompanying starvation, malnutrition, cachexia, chronic infection and tonsillectomy, and in conditions favoring decreased glycogen content of the liver cells. Sensitization of the liver to protein by injection, ingestion or trauma renders the liver more susceptible to the toxic damage of cinchophen.

According to Brugsch and Horsters³⁵ cinchophen directly stimulates the bile-forming cells and so causes an actual increased secretion of bile. In patients with biliary fistula an increased flow of bile from 200 to 300 per cent was observed. Stransky³⁶ was unable to confirm these observations, but Grunenberg³⁷ and others have reported an increase in bile in the duodenal contents as the result of administration of cinchophen to healthy individuals and patients suffering from catarrhal jaundice. Brugsch³⁸ even maintains that there is no question of cinchophen being a liver poison when given in the usual doses, unless the patient has been on a carbohydrate-poor diet, and as a result has a poor glycogen reserve in the liver. He is so sure of the innocence of the drug that he uses it for the treatment of jaundice in subacute atrophy of the liver. Taubmann³⁹ states that cinchophen is excreted in the bile and inhibits carbohydrate digestion, and does therefore favor decreased liver glycogen storage.

The study of the physiologic chemistry and clinical pathology of cinchophen and oxycinchophen, recently published by Lichtman,⁴⁰ makes some illuminating comments upon the so-called hepatotoxic

action of cinchophen. He says in part, "There is evidence, however, that a single or even repeated standard test doses of 0.45 gm. are not toxic, even in the presence of severe damage of the liver. Studies were made on a patient with degeneration of the liver attributed to the ingestion some time before of approximately 18 gm. of cinchophen in a period of 18 days. . . . Thus in this case ascribed to the hepatotoxic action of cinchophen, 3 doses of 0.45 gm. of this substance given at intervals of approximately a week had no toxic action and did not delay clinical and functional recovery. . . . Similar observations have been made in all the cases of disease of the liver that have been studied. Thus far no instance of untoward effects attributable to the cinchophen employed in the test has been countered. . . . In fact, in many instances, a decrease in the intensity of the jaundice is noted on the day following the test, which may be due to the choleretic action of the drug."

The cause of the toxicity of cinchophen has been variously discussed by Rotter,⁴¹ Willcox,⁴² Sollmann,⁴³ Sherwood,¹⁵ Crawford,⁴¹ and others. The idea variously exploited that the oxidation of the quinolin nucleus produces highly toxic nitro compounds is very improbable. It is practically exploded by the work of Lichtman above referred to, which shows the oxidation products of cinchophen; and by the work of Furth and Kuh.¹⁸ No explanation at present exists for the toxicity of cinchophen except hypothesis. The most likely and generally accepted hypothesis is that phenylcinchoninic acid, in the presence of certain predisposing conditions, may sensitize or otherwise damage liver cells in such a way as to produce acute yellow atrophy.

The author has been particularly interested in the possibility of increased toxicity when cinchophen is given in conjunction with iodine or iodids. We have attempted so far as records are available to determine what percentage of cases of toxicity due to cinchophen had taken iodids or iodine with the drug. The accompanying table, kindly prepared for me by a colleague, sets forth some of the facts in this connection. From this table it appears that 14 patients of the reported toxic cases had iodids administered with the cinchophen derivative. Of this number 6 died and the remaining 8 recovered. Five patients under observation at the present time are taking neocinchophen and potassium iodid. Four of these have had no digestive upsets, but one of them discontinued the iodid because of anorexia.

A patient recently seen at the Rockefeller Hospital, however, had been taking cinchophen for 1 week. She had been taking about 12 grains of cinchophen a day. She discontinued the cinchophen and took 5 drops of a potassium iodid solution 3 times a day for 3 or 4 days. Because of recurrence of pain she stopped the iodid and again took atophan, 8 grains a day for 8 days. Following

this period she again took potassium iodid. Seven days after taking the last dose of atophan she developed urticaria. The iodid was stopped. Three weeks later she became jaundiced. The patient recovered. It was thought that the poisoning was due perhaps to the combination of cinchophen and iodid. It is interesting that the patient, several years previous to this, had had an urticaria due to some food poisoning.

We have studied the records of 200 of our own patients who have taken either neocinchophen (tolysin) or cinchophen (atophan). (See Tables 1 and 2.) The patients have not been selected, but

TABLE 1.—TOLYSIN CHART.

Diagnosis.	No. of cases.	Previous gastrointestinal history.	Gastrointestinal effect.
Osteoarthritis	68	None	Indigestion, 2; nausea, 2; pain in stomach, 1; fainting spells, 1; dizzy, 1.
Infectious arthritis	104	Dig. upsets, 1	Nausea, 7; indigestion 5; burning in stomach, 1; rash, 3; nervousness, 2; vomiting, 1; palpitation, 1.
Neuritis	11	None	Fever, 1; nausea, 1; urticaria, 1.
Rheumatic fever	3	None	None.
Gout	1	None	None.

TABLE 2.—ATOPHAN CHART.

Diagnosis.	No. of cases.	Gastrointestinal effect.
Infectious arthritis	8	None
Osteoarthritis	6	Vomiting, 1*

* Patient who vomited after atophan had a previous history of loss of weight and appetite before taking the drug.

were consecutive admissions who had been given one of the cinchophen preparations. Most of the patients had been seen by the author. The material has been collected from private practice, St. Luke's arthritic clinic, and Post-Graduate Hospital arthritic clinic. In this series of 200, we have observed no instances of jaundice and there have been no fatalities. Fourteen had cinchophen (atophan) while 186 had neocinchophen (tolysin). Two patients had taken both cinchophen and neocinchophen. The dose varied from 15 grains in 1 day to 16,080 grains in 96 weeks. The drug in most instances was given in from 5- to 10-grain doses 3 times a day for 5 days a week. The patients in the majority of cases were also taking 3 gm. of sodium bicarbonate and the juice of a half lemon in a glass of water each day. In addition to tolysin or cinchophen, the patients were having other forms of treatment such as physiotherapy and vaccine therapy. All the patients with chronic infectious arthritis were receiving vaccine. In the appended table is recorded any history of previous gastrointestinal upsets or liver disturbances. There have been listed any digestive upsets that followed the ingestion of the drug. Of 200 patients, 22 complained of some digestive trouble. Only 2

of these vomited. One had taken 107 tablets of tolysin in 90 days while the other had taken 9 tablets of atophan. On 4 patients, not included in this series, we have determined the bile index before and after the ingestion of 150 grains of atophan. The icteric index was not found to be increased in any of these 4. Five patients developed a rash, 1 patient complained of palpitation and restlessness after he had taken 3 tablets. One fainted after she had taken 84 tablets in 2 weeks. Another developed a temperature after ingestion of 144 tablets in 4 weeks and 1 complained of extreme nervousness after he had taken 150 tablets in 25 days. One lady, aged 51 years, complained of dizzy spells after she had taken 120 tablets in 4 weeks. She stated that her pain completely disappeared with the use of tolysin, but that it made her so dizzy that she was unable to take it. However, since then she has been able to take 1 tablet a day without any difficulty. In all, 30 patients have manifested some toxic symptoms. None of these was of a serious nature, and none of the patients was confined to bed because of his symptoms. In the cases where vomiting, nausea or a rash appeared, the drug was discontinued. If the patient complained of indigestion to a very slight degree or beginning loss of appetite, he was given bicarbonate of soda in addition to the neocinchophen. If this were not satisfactory the cinchophen or neocinchophen was discontinued.

Four of the cases reported above are of such interest that they deserve more careful description.

Case Abstracts. CASE 156. A nurse, aged 28 years, developed arthritis following the birth of her child 3 years previous. About a year before she was seen in the clinic, she had taken 1200 grains of cinchophen over a period of 1 month, an average of about 40 grains a day. At the end of this time nausea developed without vomiting. She then changed to neocinchophen and during the following 2 months took 1800 grains of that drug. After this urticaria appeared. She discontinued the drug for 4 weeks and then took 10 grains of neocinchophen and developed a severe urticaria. A month later, on request, she took 1 5-grain tablet of neocinchophen and immediately developed urticaria. One week later she took 6 tablets of the same drug and developed a rash. Her urine was tested at the time to determine the optical rotation and we were unable to find any trace of cinchophen in her urine. This test and its significance will be given more in detail later in the paper.

CASE 149, aged 36 years, whose diagnosis was gout, after taking 5 grains of cinchophen became quite restless and after taking 15 grains became so nervous and his pulse became so rapid that he was given 8 minims of adrenalin. The drug was discontinued.

CASE 150, aged 38 years, who was suffering from neuritis, gave a history of sensitiveness to aspirin and all salicylic acid preparations. Five grains of aspirin would produce severe urticaria. When first tried with tolysin she took it without any ill effect. This relieved her pain and she was most grateful, but after ingestion of 48 tablets over a period of 2 weeks, she developed severe urticaria and the drug had to be discontinued.

CASE 148, aged 37 years, whose diagnosis was acute rheumatic fever, gave no history of digestive upsets until the onset of her present illness, at which time she vomited and developed an erythema. She was given

505 grains of neocinchophen without any untoward symptoms except a headache after the ingestion of 90 grains in 2 days. She was receiving 45 grains a day. She felt so well at this time that the drug was discontinued. Five days later she felt ill and again took the drug. After taking 30 grains her temperature rose to 99° F. and a rash developed. Adrenalin was given to control this. The drug was discontinued. Eleven days later 15 grains of aspirin were given and she again developed a rash.

Three of these 4 cases are reported in more detail because they lend evidence to the idea that it is possible for a patient to develop a sensitiveness to a drug which at first does them no harm. It is strange that one could take 3000 grains of cinchophen and neocinchophen without any untoward symptoms and then discontinue the drug and at some future time, even though it be a year or more distant, 5 grains of the drug would upset them. One should be doubly cautious in again administering the drug. It is most important to give a small initial dose to determine sensitivity. In reading the literature of the cinchophen poisoning cases, one is struck with the number of cases whose toxic symptoms have begun after the drug has been discontinued and then recommenced.

An attempt has been made to review the literature and determine how many of the fatal cases had taken the drug intermittently and what percentage of the toxic symptoms had occurred after the second and third courses of one of the phenyleinchoninic acid preparations. Fourteen of the 86 cases reported had an interval between their first and toxic doses. Five of these died. The results are given in Table 3.

Although no instance of acute yellow atrophy was observed in the 200 consecutive cases which were studied, yet an analysis of case histories at St. Luke's Hospital showed 2 instances of acute yellow atrophy in patients who had been taking either cinchophen or neocinchophen. Both of these patients had chronic infectious arthritis.

CASE N. S., a woman, aged 45 years, had been given atophan and neocinchophen in large doses over a period of a year or more. The exact dose cannot be determined. She entered the hospital and died on the second day. The diagnosis was acute yellow atrophy; no causative agent other than the atophan could be found. Her urine was negative for arsenic. No autopsy was obtained.

CASE B. K., a girl, aged 17 years, came to our office on November 5, 1928, and complained of arthritis of 4 years' duration. Two years prior to her visit she had had jaundice for 1 month. This was thought to be a catarrhal jaundice. She had been treated during the past 2 years at various hospitals. We have no record of the drugs which she had taken previously. She, however, stated that she had had milk and iron injections in one hospital and in another had had injections of protein which gave her chills. On November 14, 1928, she was admitted to St. Luke's Hospital to have a complete bacteriologic examination made of any foci of infections. An autogenous vaccine was prepared. On December 11 she returned to our office. Her temperature was 100° F. and she was having very severe joint pains. She was told to take 10 grains of tolysin 4 times a day. On December 18 she was given 0.03 cc. of autogenous vaccine. On December 22 she was

given 0.05 cc. of vaccine. On December 31 the patient developed a mild jaundice. She was admitted to St. Luke's Hospital on that day and a diagnosis of acute catarrhal jaundice was made. Her bile index was 186. On January 6 she became delirious and her temperature rapidly rose to 106° F. On January 7 she died, and a diagnosis of acute yellow atrophy was made. No autopsy was obtained.

It would be difficult to report this case as one of acute yellow atrophy proven to be due to tolysin because we had no autopsy, and furthermore we are not certain of the drugs she had taken before she came to us. Moreover, the patient had various protein injections and a history of jaundice, both of which are now known to be contraindications to the use of cinchophen preparations. It seems most likely, however, that this was a case of acute yellow atrophy and that the final exciting agent was tolysin. She received about 700 grains of tolysin over a period of approximately 3 weeks. This is only the second case that we have been able to find that might possibly be due to neocinchophen, and even in this case we have no absolute proof of the diagnosis.

Within the past year various investigators have sought independently to shed some light upon this toxicity question by laboratory methods. Among others we refer to Lichtman, quoted above, Churchill and von Wagoner,⁴⁵ Minot and Cutler, and my associate, Dr. A. J. Quick at Cornell University Medical School. Churchill and von Wagoner fed cinchophen to dogs in doses 27 times the calculated therapeutic dose (595 mg./K) mixed with their food. The urea nitrogen showed a marked rise, and at autopsy most of the dogs showed from one to three acute gastric ulcers and a number of yellowish areas over the surface of the liver, which on microscopic examination showed varying degrees of necrosis. Minot and Cutler^{46, 47} have experimented with the idea that acute yellow atrophy is indicated by a high blood guanidin and a low blood dextrose. They believe that calcium gluconate tends to prevent acute yellow atrophy in dogs and in human beings.

Dr. A. J. Quick has very kindly done some analyses on urines of both patients and dogs. Five patients were examined, 2 of whom took cinchophen and 3 of whom took neocinchophen. The urines of the patients receiving cinchophen showed under polariscopic study a negative rotation directly proportional to the output of cinchophen. The neocinchophen urines, although the patients had received 30 grains a day for 7 days prior to collection of the specimen, produced no rotation of the plane of polarized light.

The author was one of the two who took the cinchophen. Urine was collected for 1 hour previous to the ingestion of 2 gm. of cinchophen. Blood uric acid was determined at this time on a fasting stomach. The uric acid was found to be 5.1 mg. per 100 cc. The volume of urine collected was 70 cc. The negative rotation was 0.15. One hour after the ingestion the volume of urine was 55 cc. and the negative rotation was 0.2. The blood uric acid was found

to be 4.3 mg. per 100 cc. Two hours after the ingestion of the cinchophen the volume of urine was 40 cc. and the negative rotation was 0.2. Three to 6 hours later the volume of urine passed was 140 cc. and the rotation was 0.35. The remainder of the 12-hour specimen which was collected showed a rotation of 0.2. From this observation it can be concluded that little if any of the cinchophen is excreted until 3 hours after its ingestion and that most of it is excreted 3 to 6 hours after the ingestion of the drug.

Experimental. Four dogs have been studied. The first dog weighed 8.4 kilos. She was given daily 5 gm. of cinchophen mixed with food scraps. Her appetite remained normal until the fifth day when she refused food and began to have severe diarrhea. She became very emaciated and would probably have died, if left unattended. For several days the dog was given nourishment by stomach tube and forced feeding; on the fourth day she again ate. Twelve days after the first dose of cinchophen was given the dog was normal, but still emaciated. At that time the dog was given sodium benzoate, which was conjugated normally. This we took to indicate that the liver was normal. Her urine had, throughout the experiment, marked levorotation. The second dog weighed 14.9 kg. She was fed a diet of casein, lard and sucrose and 5 gm. of cinchophen at 10 A.M. Eighty cubic centimeters of urine were collected from 10 A.M. to 4 P.M. The rotation was 1.10. From 4 P.M. to 10 P.M. 60 cc. of urine were collected. This had a negative rotation of 1.50; from 10 P.M. to 10 A.M. the next morning 93 cc. of urine were collected and the rotation was 2.00. The urine was first clarified with activated charcoal. The nature of the optically* active compound has not as yet been determined. It was first thought that the cinchophen was conjugated with glycuronic acid and that this conjugated substance was presenting the negative rotation. The third dog was given $2\frac{1}{2}$ gm. of cinchophen by stomach tube. Three hours later the dog vomited. Three days later he was again given $2\frac{1}{2}$ gm. by stomach tube. He developed marked tremor and seemed completely prostrated. He made complete apparent recovery in 6 hours. The next day he had no appetite. His icteric index was normal. The urine showed marked levorotation. The fourth dog was given 5 gm. of neocinchophen. This did not affect him in any way nor did his urine produce levorotation.

While the work of Lichtman has to a certain extent clarified the question of the excretion products of cinchophen, Dr. Quick and the author will attempt to pursue this study further in a laboratory way and report at a later date upon the products of cinchophen decomposition and the possibility of their conjugation with glycin.

Summary. 1. A study of 200 cases taking neocinchophen or cinchophen has been made. No fatal results were observed in these 200 cases, but 30 had some slight digestive or circulatory upsets. None was jaundiced.

2. A preliminary study on the excretion of cinchophen and neocinchophen preparations in human beings and dogs yielded the definite result that cinchophen develops a levorotary activity in the urine. In human beings most of the cinchophen is excreted within 3 to 6 hours after ingestion. In the urine of animals taking neocinchophen no such substance has been found.

* Optical rotation is expressed in degrees in 1-dm. tube.

3. The superiority of neocinchophen to cinchophen for general clinical use appears at the present time a fair conclusion from the evidence of the literature and the author's cases.

NOTE.—The writer wishes to acknowledge his indebtedness to Dr. R. H. Boots for his many helpful suggestions, to Dr. A. J. Quick for his laboratory studies and aid in the preparation of the laboratory portion of this paper, and to Dr. D. A. Bryée, Medical Director of the Calco Chemical Company, for his aid in the preparation of bibliography and tabulations upon the subject of phenylcinchoninic toxicity.

BIBLIOGRAPHY.

1. Doebner, O., and Gieseke, M.: *Justus Liebig's Ann. der Chem.*, 1887, **242**, 291.
2. Nicolaier, A., and Dohrn, M.: *Deutsch. Arch. f. klin. Med.*, 1908, **93**, 331.
3. Phillips, J.: *J. Am. Med. Assn.*, 1913, **61**, 1040.
4. Schroeder, K.: *Ugesk. f. Laeger*, 1922, **84**, 1141.
5. Worster-Drought, C.: *Brit. Med. J.*, 1923, **1**, 148.
6. Reichle, H. S.: *Arch. Int. Med.*, 1929, **2**, 281.
7. Rabinowitz, M. A.: *J. Am. Med. Assn.*, 1930, **95**, 1228.
8. Cabot, R. C.: *Boston Med. and Surg. J.*, 1925, **191**, 1122.
9. Grolnick, M.: *Med. J. and Rec.*, 1930, **132**, 240.
10. Editorial, *J. Am. Med. Assn.*, 1929, **89**, 1167.
11. Walker, W. G.: *New England J. Med.*, 1931, **204**, 253.
12. Parson, L., and Harding, W. G.: *AM. J. MED. SCI.*, 1931, **181**, 115.
13. Personal communication.
14. Ross, J. B.: *Canad. Med. J.*, 1931, **24**, 632.
15. Sherwood, K. K., and Sherwood, H. H.: *Arch. Int. Med.*, 1931, **48**, 82.
16. Rotter, L.: *Ztschr. f. exp. Path. u. Therap.*, 1918, **19**, 1917.
17. Hanzlik, P. J., Scott, R. W., Widenthal, C. N., and Fettermann, J.: *J. Am. Med. Assn.*, 1921, **26**, 1728.
18. Furth, O., and Kuh, E.: *J. Pharmacol. and Exp. Ther.*, 1930, **38**, 57.
19. Hanzlik, P. J.: *Medicine*, 1926, **5**, 306.
20. Mendel, B.: *Deutsch. med. Wehnschr.*, 1922, **48**, 829.
21. Starkenstein, E.: *Ibid.*, p. 1161.
22. Dohrn, M.: *Klin. Wehnschr.*, 1923, **2**, 819.
23. Graham, G.: *Proc. Roy. Soc. Med.*, 1926, **20**, 257.
24. Griesbach, W., and Lamson, G.: *Biochem. Ztschr.*, 1919, **94**, 277.
25. Starkenstein, E.: *Biochem. Ztschr.*, 1920, **106**, 172.
26. Pulay, E.: *Med. Klin.*, 1929, **25**, 1212.
27. Bendix, H.: *Therap. d. Gegenw.*, 1912, **53**, 301.
28. Jokl, R. H.: *Prag. med. Wehnschr.*, 1914, **23**, 200.
29. Chace, A. F., Myers, V. C., and Killian, J. A.: *J. Am. Med. Assn.*, 1921, **77**, 1230.
30. Barbour, H. G., Lozinsky, E., and Clements, C.: *AM. J. MED. SCI.*, 1923, **165**, 708.
31. Boots, Ralph H., and Miller, C. P., Jr.: *J. Am. Med. Assn.*, 1924, **82**, 1028.
32. Poynton, F. J.: *Lancet*, 1928, **2**, 637.
33. Chace, A. F., and Fine, M. S.: *J. Am. Med. Assn.*, 1914, **63**, 945.
34. Evans, G., and Spence, A. W.: *Lancet*, 1929, **216**, 704.
35. Brugsch, T., and Horsters, H.: *Ztschr. d. ges. exp. Med.*, 1924, **43**, 517.
36. Stanskey, E.: *Biochem. Ztschr.*, 1925, **155**, 256.
37. Grunenberg, K., and Ullman, H.: *Med. Klin.*, 1924, **20**, 663.
38. Brugsch, T.: *Therap. d. Gegenw.*, 1928, **1**, 14.
39. Taubmann, G.: *Arch. f. exp. Path. u. Pharmakol.*, 1927, **121**, 204.
40. Lichtman, S. S.: *Arch. Int. Med.*, 1931, **48**, 98.
41. Rotter, L.: *Chemical Abstr.*, 1918, **12**, 2384.
42. Willcox, W. H.: *Brit. Med. J.*, 1926, **2**, 273.
43. Sollmann, T.: *Manual of Pharmacology*, 2d ed., Philadelphia, W. B. Saunders Company, 1922, p. 569.
44. Crawford, T.: *Brit. Med. J.*, 1918, **1**, 450.
45. Churchill, T. P., and Von Wagoner, F. H.: *Soc. Exp. Biol. and Med.*, 1931, **28**, 581.
46. Minot, A. S., and Cutler, J. T.: *J. Clin. Invest.*, 1928-1929, **6**, 369.
47. Minot, A. S., and Cutler, J. T.: *Proc. Soc. Exp. Biol. and Med.*, 1929, **26**, 607.

REVIEWS.

A HANDBOOK OF OCULAR THERAPEUTICS. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago, etc. Pp. 272; 36 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$3.25.

THE author has prepared a concise résumé of the nonsurgical methods of treatment used in ophthalmology. The first five chapters deal with the equipment advisable for routine ophthalmic practice, the commoner drugs and organ extracts used in ophthalmology, the value of specific and non-specific protein therapy, and certain forms of physical therapy such as light, diathermy, the thermophore, Roentgen ray and radium. The action of the various drugs is described whenever this is known but many remedies are advised empirically with the frank statement that as yet we have no knowledge of their pharmacodynamics.

Practical application is made wherever possible of modern chemistry, for example, the authors advises making up various drugs in buffered solutions. The following solution is recommended for pilocarpin, zinc salts, cocain and adrenalin:

Boric acid	6.2 gm.
KCl	7.4 gm.
H ₂ O	1000 cc.

This is an acid buffer solution with a pH of 5.5. A similar solution is recommended as a solvent for holocain with the addition of a few drops of dilute acetic acid. The following solution is recommended as a vehicle for atropin, homatropin, eserin and scopolamin:

Sodium bicarbonate	21.2 gm.
H ₂ O	1000 cc.

This is a slightly alkaline buffer solution with a pH of 7.6. A third medium which acts as a neutral buffer is a 3 per cent solution of gelatin in a solution of water. This is recommended as a vehicle for antiseptics, since they are less irritating in this form than in aqueous solutions and the gelatin spreads in a thin film over the conjunctiva and remains in contact with it longer than aqueous solutions. The author gives his routine method for the administration of tuberculin therapeutically.

The last 11 chapters deal with the treatment of diseases of the eye arranged in anatomic order, as diseases of the lids, conjunctiva, cornea, uveal tract, etc. The author's point of view recommending a new procedure is best exemplified by the following paragraph in the introduction:

"A position of therapeutic nihilism, or of unreasoning scepticism with regard to new agents and methods, is equally fallacious, as in the position of resting content with time-honored methods, some of which have nothing but the sanction of years to justify their continued use."

F. A.

LES MALADIES DE L'ESPRIT ET LEURS MÉDECINS DU XVI^e AU XIX^e SIÈCLE. By M. LAIGNEL-LAVASTINE and JEAN VINCHON. Pp. 377; illustrated. Paris: Norbert Maloine, 1930.

THIS handsome volume aims to delineate the principal stages in the evolution of psychiatry in the last four centuries. Realizing that this specialty may be studied not only in the bodies of patients but also in their writings, paintings or in fact in any objective creation of their diseased minds, the authors rightly emphasize the practical clinical value of the historic method, as well as its cultural edification. Their plan of procedure is to present some 24 essays, arranged according to the chronology of the subject matter and joined together by the guiding motif already mentioned. Thus in the 16th century chapters von Schenck, von Grafenberg and Paré present their neuropsychiatric concepts, to be followed by essays on the genesis of modern ideas of the insane, incubi, etc. In the 17th century, Willis, Ettmüller, Diemerbroeck and Zacchias are covered; while in the 18th, de la Metterie, the encyclopedists, Hecquet, animal magnetism and the precursors of Boyle furnish the subject matter. Pinel is taken as the representative of the 19th century and the volume concludes with an essay on the evolution of the treatment of the psychoses.

E. K.

HISTORY OF MEDICINE IN THE UNITED STATES. By FRANCIS R. PACKARD, M.D., Editor, *Annals of Medical History*. 2 vols. Pp. 1323; 103 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$12.00.

It is now 30 years since the first edition of this work appeared; for many of these years it has been out of print, yet it is still the only book covering the subject as a whole. The new edition has, therefore, been awaited with interest for some time and it now appears considerably enlarged and in a new format of two stately volumes of Hoeber's well-known dark blue. Nevertheless, "no attempt has been made to consider the wonderful things accomplished by the great foundations for research, medical education and hygiene which have come into being in the United States in late years, their origin being too recent to permit of their being included in a work which purports to be truly historical"; neither has it seemed advisable to the author to change to any extent the method of approach of the former edition which is partly chronological and partly by special topic. Thus in the first volume after a chapter on colonial medicine, the other 8 chapters treat of epidemics in the English colonies up to 1800, medical legislation, the earliest hospitals, pre-scholastic medical education, the earliest schools, pre-Revolutionary publications, Revolutionary medicine and Army medicine to the close of the Spanish War (this last written by Colonel Ashburn thus unfortunately not including the splendid story of the conquest of yellow fever). The second volume opens with a chapter by Lieut. Commander Parsons on the medical department of the U. S. Navy, followed by others on some of the medical schools founded during the first half of the nineteenth century, outlines of the development of medical practice and education in some of the states, foreign influences on American medicine, some notable events in American medicine and surgery, and the beginnings of specialism in America. A series of 11 useful Appendices, mostly on eighteenth century matters, also includes useful information on the Ether Controversy, Women in Medicine and notes on regular and irregular Medical Schools in the United States. A bibliography of 24 pages and 2 good indexes complete the value of the work.

REGARD for the personality of the author, his individual historical contributions and the great service he is rendering to medical history through

the Annals of Medical History, all make it difficult to appraise this work objectively. However, all must concede that it was and now, still more, is the most important existing book on the history of American medicine. The author has apparently not intended it to be in any sense a complete record of events either in form or quantity and in the Preface himself points out its unevenness and its omissions. While we can only regret that a person so eminently fitted for the job has not been permitted by the rigors of "chasing that damned guinea" to produce an adequate history in the conventional sense, we can be thankful for this series of vivid narrations and evaluations, covering so many phases of American medicine in such an interesting way. Let us hope that before another 30 years have passed, a well-earned repose will permit the author to add to his material and rearrange it into a standard history that will take rank with such great American works as Garrison's History, Cushing's Life of Osler and Sarton's Introduction to the History of Science.

E. K.

ROENTGENOLOGIC STUDIES OF EGYPTIAN AND PERUVIAN MUMMIES. Anthropology Memoirs. Vol. III. By ROY L. MOODIE, Paleopathologist to the Wellcome Historical Museum, London. Pp. 62; 76 plates in photogravure, chiefly from roentgenograms. Chicago: Field Museum of Natural History, 1931. Price, \$5.00.

THE author's widely known works on paleopathology are well supplemented by this roentgenologic study of Egyptian and Peruvian mummies made in the Division of Roentgenology of the Field Museum. In spite of occasional obscuration caused by dense embalming materials or objects included in the coffin, or by other technical difficulties, the beautifully made and beautifully reproduced pictures show a considerable number and variety of diseases. The author estimates that "among the pre-Columbian Peruvian mummies the incidence of disease and injury is 10.52 per cent," with 40 per cent among the Egyptians; though his numbers are really much too small for statistic solidity. Although the body of the text is chiefly occupied by detailed descriptions of the 53 mummy packs studied, there are interesting summaries of the Development of Roentgenologic Study of Mummies, Peruvian Mummification, Pre-Columbian Pediatrics and similar topics. The Field Museum is to be congratulated on this valuable production with its splendid reproductions.

E. K.

THE ETHNO-BOTANY OF THE MAYA. Publication No. 2 of the Tulane University of Louisiana, Middle American Research Series. By RALPH L. ROYS. Pp. 359. New Orleans: The Department of Middle American Research, The Tulane University of Louisiana, 1931.

WE have elsewhere made the statement that medical aspects of the Mayan civilization constitute an appropriate and probably a fruitful field for the new school of medical historians in this country to pursue. From this point of view the present volume assumes new importance. Coming at a time when the Mayan culture is being actively explored in various ways, it gives a scholarly presentation of a field that, except for the work of the Heye Foundation and the Peabody Museum, has had but little attention from American schools. The survey of Mayan materia medica is classified under some two score groups of diseases such as Poisoning, Ear Complaints, Skin Diseases, Ulcers, Abscesses, Cancer and Tumors (the largest section), etc. In each case the Mayan prescription is first given (a key to pronuncia-

tion being provided), and the English translation following. A list of Mayan fanna names and an extensive bibliography add to the usefulness of the book. We congratulate Tulane on this praiseworthy production.

The following publications have already been published or are about to appear in this series: Tribes and Temples, by Frans Blom and Oliver LaFarge, II; the Year-Bearer's People, by Oliver LaFarge, II, and Douglas Byers; Miscellaneous Papers Pertaining to Research in Middle America, written by friends and the staff of the Department of Middle American Research of Tulane University; Herman Beyer on Maya Hieroglyphs; Frans Blom on the Ruins of Uxmal, Yucatan; Miscellaneous Linguistic Manuscripts in the Library of the Department of Middle American Research of Tulane University. E. K.

THE FACTOR OF INFECTION IN THE RHEUMATIC STATE. By ALVIN F. COBURN, Resident Physician, Presbyterian Hospital, New York City. Pp. 288; 48 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$6.00.

A CONCISE, thorough, scientific study of the rôle of infection in the rheumatic state. The material is ably presented, in a well illustrated and printed book. An important contribution to the subject. G. W.

CLINICAL OBSERVATIONS ON THE SURGICAL PATHOLOGY OF BONE. By DAVID M. GREIG, M.B., C.M., F.R.C.S. (EDIN.), F.R.S.E., Conservator of the Museum of the Royal College of Surgeons of Edinburgh. Pp. 248; 224 illustrations. Edinburgh: Oliver & Boyd, 1931. Price, 30/- net.

In this beautifully illustrated monograph are presented the opinions of a clinical surgeon upon the more common bone lesions. An attempt is made to condense and correlate a number of the formerly uncorrelated pathologic processes of bone disease.

The works of Leriche and Policard have strongly influenced the opinions of the author, many of whose views are unorthodox.

The monograph is interesting and well worth serious study. An easily following style facilitates the reading of the treatise. G. W.

CONTROL OF CONCEPTION. By ROBERT LATOU DICKINSON and LOUISE STEVENS BRYANT. Pp. 290; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.50.

THE book is a most careful and detailed compilation of all that is at present known upon the subject of the control of conception. Each phase of this many-sided problem is reviewed and scrutinized in a most scholarly and impartial fashion. The collective experience of many sources of information is set forth in due order and with painstaking care. The whole text is liberally illustrated with exceedingly clear illustrations, of a semidiagrammatic nature, all accurately drawn to scale.

The subject matter is presented in nine chapters which are as follows: An introduction; a detailed and careful review of the anatomy and physiology of the generative organs of both sexes; the technique of contraception—a long chapter in which all known methods are presented and evaluated; the next three chapters, on sterilization without unsexing, early

therapeutic abortion, sterilization and contraception, are brief and lucid; the final three chapters, on clinic organization and service, the legal status of contraception and sterilization, and the general philosophy of contraceptive methods, are an admirable charting of the facts, actually learned by experiences in this rather nebulous and neglected branch of science. The keynote of the book is sounded in the final chapter, in which the authors stress the incompleteness of our knowledge and pleads for further organized coöperation from many agencies to complete our information. O. T.

TUMORS OF BONE. By CHARLES F. GESCHICKTER, M.D., Surgical Pathologic Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore, and MURRAY M. COPELAND, M.D., Memorial Hospital, New York City. With Forewords by DEAN LEWIS, M.D., and JOSEPH COLT BLOODGOOD, M.D. Pp. 709; 406 illustrations. New York: The American Journal of Cancer, 1931. Price, \$5.00.

HERE is a monumental and pioneer work on bone tumors. The work is of importance chiefly because of the critical analysis of the subject and the excellent condensation and correlation of the material. Much of the book has appeared during the past year and a half in the Archives of Surgery. G. W.

THE FUNDUS OF THE HUMAN EYE. By ERNEST CLARKE, C.V.O., M.D., F.R.C.S., Consulting Surgeon to the Central London Ophthalmic Hospital, etc. Preface and Table of Contents, with 51 colored plates. New York: Oxford University Press, 1931.

THIS book is composed of a series of 51 illustrations of the fundus oculi by the Editor of the *Haab's Atlas of Ophthalmoscopy*. The illustrations are taken from a collection of paintings owned by Hamblin Company and are generally very good. The descriptions of the plates are too scant. F. A.

IMHOTEP TO HARVEY. BACKGROUNDS OF MEDICAL HISTORY. By C. N. B. CAMAC, M.D., Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University. Foreword by HENRY FAIRFIELD OSBORN, Sc.D., LL.D. Pp. 324; 2 figures. New York: Paul B. Hoeber, Inc., 1931. Price, \$3.75.

THE present volume, as its subtitle implies, may well be used as an introduction to the subject of medical history, which later perhaps may be read in greater detail piecemeal or in larger works. The basis of the author's well-known Seminars in the library of the College of Physicians, it aims at and succeeds in presenting a comprehensive outline, of which the body or any part of it can be filled in by the individual *ad lib*. Thus biographic details are conspicuous by their absence. Imhotep, for instance, appears on the title page and list of books only, while both the historical settings of the different periods and the other sciences related to medicine are treated with corresponding liberality. This tends toward a closely woven argument, relatively unencumbered by too many obstructing details, and promotes continuous reading. Most of the 10 chapters are chronologic, though they are preceded by one on the Evolution of Inquiry

and followed by another on Schools of Thought in Medicine, while an especially interesting discussion of the Environment of the Inquirer in the Mediæval and Renaissance Periods follows these two chapters. The chronologic chapters are each preceded by a useful table, subdivided into "Pursuits," "Medical Practice Based On," "Records," "Writers and Teachers." Appendices of Historic Records (in continuation of an earlier work of the author's) and a List of Books are as welcome as the lack of an index is regretted. A curious printer's pie at the bottom of page 69 is one of the few slips in a book which in type, paper, proportions and binding continues the high standard of Hoeber's blue series. We believe that this will prove for most readers the most instructive and entertaining of any of the smaller books covering the whole field of the history of medicine.

E. K.

THE PRACTICE OF CONTRACEPTION. Edited by MARGARET SANGER and HANNAH M. STONE, M.D., with a Foreword by ROBERT L. DICKINSON, M.D. Pp. 300; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.00.

THIS book is an international symposium and survey of the practice of contraception, the material being taken from the proceedings of the Eleventh International Birth Control Conference, held at Zürich, Switzerland, in September, 1930. The material which consists of papers on various phases of contraceptive practice, both practical and experimental, and the discussions these papers provoked, is divided into four main headings: The first deals entirely with actual methods of contraception practice—it takes 175 pages; the second deals with abortion only, and takes only 25 pages; the third gives detailed description of the operations of the existing birth control clinics in the various countries and their struggles in coming into existence; the fourth is a summary of the material already presented.

The book is of extreme interest to anyone already well informed on various phases of contraceptive practice. The views expressed by the various authors in the papers and discussions are of so conflicting a nature as to make the book unsuitable for a textbook or guide to a practitioner.

O. T.

MANUAL OF SURGERY. VOL. II. EXTREMITIES: HEAD AND NECK. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 685; 303 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, \$3.80.

ABOUT one-half of the volume is given over to a discussion of fractures and orthopedic diseases. The discussion of fractures in general is improved over that found in the earlier editions but the methods suggested and the illustrations in many cases do not come up to the standard of American texts. Brief discussions of injuries and diseases of the skull and brain are followed by a description of the diseases of the spine and spinal cord. The final chapters of the book treat of the surgical conditions of the face, mouth, ears and neck. A rather complete chapter is given on the thyroid gland. The book has been brought up to date in many respects but many of the illustrations are poor and no attempt has been made to recommend some of the more recent operative methods.

L. F.

MANUAL OF SURGERY. VOL. III. THORAX AND ABDOMEN. By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 578; 177 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, \$3.80.

THE first part of the book treats of diseases of the chest, heart and breast. Then follows a more complete discussion of the diseases of the abdomen and pelvis. Peritonitis, appendicitis, hernia, diseases of the stomach, intestinal obstruction and diseases of the colon, rectum and anus are described in the order named. This portion of the book has been completely revised and numerous excellent illustrations have been added. The chapter on Diseases of the Liver and Bile Passages has been brought to date. A very short chapter on Intra-abdominal Gynecologic Conditions is followed by a long section on genitourinary diseases. The method by which each section is introduced is the same in all of these volumes. A brief discussion of the anatomy and physiology of the part is presented, followed by a section on the methods of investigation and of critical examination of the organ under consideration. Various clinical tests are outlined in this section and, finally, there is appended a list of definitions describing the names of the operations performed on the organ. This revision of the standard surgery of Thomson and Miles again modernizes this system of surgery. It does not attempt to describe any of the operative methods. It should be found useful, as it has been in the past, as a ready reference on the subject of surgical diseases.

L. F.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. VIII. FUNGI, STREPTOTHRICEÆ, SPIROCHÆTES, NORMAL FLORA, SWINE ERYSIPELAS. By VARIOUS AUTHORS. Pp. 389; illustrated. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set, £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th St., New York.

A REMARKABLY rich fund of information is contained in the 389 pages. The concise, pointed English style of previous volumes is continued in this one; the frank, critical attitude is welcome in view of the authority behind it. The chapters cover the following subjects: Fungi Pathogenic to Man; Actinomycosis and Similar Conditions; Pathogenic Leptothricæ; The Spirochætes; Commensal Spirochætes; Blood Spirochætes; Syphilis; Rat-bite Fever or Sodoku; The Leptospiroses; Yaws; The Normal Bacterial Flora of Man; Swine Erysipelas.

The chapter on Pathogenic Fungi has been long awaited by English-speaking peoples. It is valuable because the viewpoints both of the systematic botanist (Ramsbottom) and the clinical pathologist (Whitfield) are submitted.

The Reviewer notes a few typographic errors, as in the spelling of "dermatitidis" and of "fulanensis" on page 20. The distinction between actinobacillosis and actinomycosis properly receives emphasis, an entire section being devoted to actinobacillosis.

Syphilis is brought down to date, including discussion of involution forms of *T. pallidum*. Singularly, "spirocheta" is permitted in preference to "treponema" in a systematic treatise such as a *System of Bacteriology*; "it seems most convenient here to refer to it as '*S. pallida*'" (page 187) is offered in extenuation.

The section on yaws includes the immunologic relationships with syphilis. A most welcome chapter is that on the normal bacterial flora of man. This

covers the skin, mouth, respiratory tract, vagina and the gastrointestinal tract.

The important section on spirochetes is the only one covered by illustrations; perhaps the lack of illustrations is the most serious criticism of the entire work, although a fuller index would help in many places. No doubt these shortcomings are enforced by a policy directed in favor of a compact volume.

The final chapter, on Swine Erysipelas, represents an abstract *in extenso* of much-scattered material in the literature.

The volume is a praiseworthy and most welcome addition to the armamentarium of English-speaking physicians—both laboratory and clinical; in fact, it is hard to see how the up-to-date laboratory man who is limited to the English language could fairly do without the subject matter it contains.

F. W.

THE STORY OF MEDICINE. By VICTOR ROBINSON, M.D., Professor of History of Medicine, Temple University School of Medicine, Philadelphia. Pp. 527. New York: Albert and Charles Boni, 1931. Price, \$5.00.

THIS book is aptly named. Though covering the whole period of medicine in 12 conventionally divided chapters, it is rather an entertaining, chronologically arranged combination of stories and quotations than a detailed exposition like the more customary histories of medicine. The author's wide knowledge, his flair for the curious yet characteristic, and his ability to paint a vivid picture have combined to produce a work that welds a wealth of historical lore to an entertaining narrative such as may not be found in any other work in this field. "When a king is the librarian of his nation, the results are astonishing;" "the silent Sphinx of Giza gazes eastward over the Nile Valley and has no message for the younger nations;" "with such gibberish Cato the Censor kept Hippocrates at bay;" "their (the ancients) utter disregard for quotation marks has wrinkled the brow of posterity;" "the laughter of Molière was the savior of medicine in the seventeenth century" may serve as characteristic aphorisms to illustrate the piquancy of this interesting production. With so much to praise, it may appear as carping criticism to observe that "the vapor of ether that has spread like a benediction" first arose for anesthetic use, not from the Massachusetts General Hospital, but from a Georgia village, and that "the alien from Japan" unfortunately did not discover the germ of yellow fever in Ecuador. The author's free use of quotations promotes a desirable first-hand acquaintance with his heroes, while the frequent inclusion of border topics, such as astrology, scholasticism, university education, botany, Renaissance art, electricity, evolution and so on, tends to a breadth of treatment that adds both to the charm and value of this highly praiseworthy production.

E. K.

MANUAL FOR THE JEWISH DIABETIC. By WILLIAM S. COLLENS, B.S., M.D., Assistant Chief, Diabetic Clinic, United Israel Zion Hospital. Foreword by HENRY JOACHIM, M.D., Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn. Pp. 138; 21 illustrations. New York: Bloch Publishing Company, 1931.

LIKE similar primers, this volume endeavors to give the patient a clear idea about diabetes. The author discusses the causes of diabetes, its complications, the method of urinalysis, the usual facts concerning the use of insulin, proper hygiene and the dietetic management. Food values, recipes and menus are given with special consideration for the Jewish diabetic. The description of the technique for testing the urine for sugar and that describing how to take insulin are unusually well done because each step is illustrated. The book is well written and comprehensive and is recommended for Jewish patients.

L. J.

BOOKS RECEIVED.

NEW BOOKS.

- Fungous Diseases.* By HARRY P. JACOBSON, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With Introductions by JAY FRANK SCHAMBERG, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and HOWARD MORROW, M.D., Clinical Professor of Dermatology, University of California Medical School. Pp. 317; 153 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$5.50.
- Nursing in Nervous Diseases.* By JAMES McCONNELL, M.D., Neurologist to the Philadelphia General Hospital; Associate Professor of Neurology, Graduate School of Medicine, University of Pennsylvania. Pp. 153; 24 illustrations. Philadelphia: F. A. Davis Company, 1932. Price, \$1.50.
- Introduction to Dermatology.* By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Diseases of the Skin, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., Visiting Dermatologist to the Kansas City General Hospital. Pp. 565; 183 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$5.00.
- Classic Descriptions of Disease.* By RALPH H. MAJOR, Professor of Medicine, University of Kansas School of Medicine. Pp. 630; 127 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.50.
- The Surgical Clinics of North America, Vol. 12, No. 4 (Mayo Clinic Number, August, 1932).* Pp. 227; 79 illustrations. Philadelphia: W. B. Saunders Company, 1932.
- The Sputum.* By RANDALL CLIFFORD, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Pp. 167; 21 illustrations and 7 plates in color. New York: The Macmillan Company, 1932. Price, \$4.00.
- The Science of Signs and Symptoms.* By ROBERT JOHN STEWART McDOWALL, D.Sc., M.B., F.R.C.P. (EDIN.), Professor of Physiology, King's College, University of London, etc. Pp. 440; 6 illustrations. New York: D. Appleton & Co., 1932. Price, \$7.00.
- Clinical Endocrinology of the Female.* By CHARLES MAYER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and LEOPOLD GOLDSTEIN, M.D., Demonstrator of Obstetrics, Jefferson Medical College, etc. Pp. 519; 117 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.00.
- Clio Medica, Vol. III, Physical Therapy.* By JOHN S. COULTER, M.D., Assistant Professor of Physical Therapy, Northwestern University Medical School, Chicago. Pp. 142; 15 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, \$1.50.
- Functional Disturbances of the Heart.* By HARLOW BROOKS, Attending Physician, Fourth Medical Service, Bellevue Hospital, etc. Pp. 288. Philadelphia: J. B. Lippincott Company, 1932. Price, \$5.00.
- A Textbook of Pathology.* By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIP. PSYCH., F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 946; 287 engravings and 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

Orthopedics in Childhood. By WILLIAM L. SNEED, M.D., Attending Surgeon, Hospital for the Relief of the Ruptured and Crippled, etc. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 318; 145 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$5.00.

Posture. By FRANK D. DICKSON, M.D., Orthopedic Surgeon, St. Luke's Hospital and the Kansas City General Hospital. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 213; 118 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$5.00.

Functional Disorders of the Gastrointestinal Tract. By WILLIAM GERRY MORGAN, M.D., F.A.C.P., Professor of Gastroenterology, Georgetown University Medical School, etc. Every Day Practice Series, edited by HARLOW BROOKS, M.D. Pp. 259; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$5.00.

Publications of the Committee on the Costs of Medical Care. No. 17. Nursing Services and Insurance for Medical Care in Brattleboro, Vt. By ALLON PEEBLES, PH.D., and VALERIA D. McDERMOTT. With an Evaluation of the Nursing Program by VIOLET H. HODGSON, R.N., Assistant Director, and KATHARINE TUCKER, R.N., General Director, of the National Organization for Public Health Nursing. Pp. 65. No. 18. *The Medical Service of the Homestake Mining Company.* By LOUIS S. REED, PH.D. Pp. 54. Chicago: University of Chicago Press, 1932. Price, 60c each.

The Cardiac Output of Man in Health and Disease. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Physiology in the Medical School of the Johns Hopkins University. Pp. 325; 14 figures and 57 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, \$4.00.

The Advance of Medicine. By RT. HON. LORD MOYNIHAN, K.C.M.G., C.B., President, Royal College of Surgeons of England. Pp. 64. New York: Oxford University Press, 1932. Price, \$1.00.

In Memoriam. Army Medical Bulletin No. 27. Supplement to Vol. I of the Medical Department of the United States Army in the World War. Pp. 37. Carlisle Barracks, Pa.: Medical Field Service School, 1932.

NEW EDITIONS.

A Descriptive Atlas of Radiographs. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S. (EDIN.). Pp. 552; 767 illustrations. Second edition revised and enlarged. St. Louis: The C. V. Mosby Company, 1932. Price, \$13.50.

Minor Surgery. By FREDERICK CHRISTOPHER, S.B., M.D., F.A.C.S., Assistant Professor of Surgery at the Northwestern University Medical School, Chicago. With a Foreword by ALLEN B. KANAVEL, M.D., F.A.C.S., Professor of Surgery at the Northwestern University Medical School. Pp. 998; 687 illustrations. Second edition reset. Philadelphia: W. B. Saunders Company, 1932. Price, \$10.00.

Essentials of Pediatric Nursing. By RUTH ALICE PERKINS, R.N., B.S., Graduate of Children's Memorial School of Nursing, Chicago, etc. Pp. 467; 55 engravings and 6 full-page colored plates. Second edition revised and enlarged. Philadelphia: F. A. Davis Company, 1932.

Handbook of the Vaccine Treatment of Chronic Rheumatic Diseases. By H. WARREN CROWE, D.M., B.Ch. (OXON.), M.R.C.S., L.R.C.P., Director of the Charterhouse Rheumatism Clinic, etc. Pp. 79. Second edition. New York: Oxford University Press, 1932. Price, 80c.

L'Inspection Médicale des Écoles. By DOCTEUR MAURICE DUVERNOY, Professeur à l'École de Médecine de Besançon; Directeur de l'Institut d'Éducation Physique de Franche-Comté. Pp. 236. Second edition. Besançon: V. Chicandre, 1932.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Nature of Allergy in Tuberculosis as Revealed by Tissue Culture Studies.—It might be well to note some additional experimental evidences concerning the rôle of allergy in the production of adult tuberculosis, bearing in mind that there are many to whom this conception of tissue reaction in tuberculosis is not acceptable. In this present study (RICH and LEWIS, *Bull. Johns Hop. Hosp.*, 1932, 50, 115) living cells from animals rendered allergic to old tuberculin were studied. These cells were washed and contrasted with cells from normal animals in plasma from the allergic as well as the normal, treated with a preparation of old tuberculin. Marked damage was done to the allergic cells by the tuberculo-protein. It is clear from these studies that the living cells from the allergic tuberculous animal, even when washed, retain their hypersensitivity to tuberculin when separated from the body by means of tissue culture. From direct findings "neither the circulatory, nervous nor other mechanisms dependent upon the intact body are necessary for the production of allergic damage." The antibody is attached intimately to the cell itself.

Insulin Therapy.—When insulin was first used in the treatment of diabetes frequently there occurred rather severe skin reactions. It soon became apparent that most of these reactions were due to chemical irritants contained in the pancreatic extracts. There was fear in the early days of insulin that there might occur severe allergic reactions, particularly in those individuals who already had insulin and then were obliged to discontinue it. This fear was not substantiated, however, and insulin therapy has been used extensively for nearly a decade now without record of any known fatality as a result of allergic reactions in sensitized individuals. However, reports of cases of insulin hypersensitiveness have appeared from time to time and undoubtedly local reactions occur in a considerable number of instances. Lawrence is

quoted as saying that such reactions occur in 20 per cent of his cases, whereas Joslin is recorded as stating that local reactions occur in about 10 to 20 per cent of his cases during the first weeks of treatment, although systemic reactions average 1 in 1000 diabetics. There is apparently an increasing number of individuals who have some local reaction to the injection of insulin. This statement is confirmed by an article written by ALLAN and SCHERER (*Endocrinology*, 1932, 16, 417), who have made a statistical study of the incidence of insulin allergy in the Mayo Clinic and found that allergic reactions are on the increase. In 1927, for example, of 428 patients treated 14 showed such reaction, a percentage of 3.2, whereas in 1930 of 401 patients treated 56 had allergic reactions, a percentage of 13.8, and in the first 6 months of this year 14.1 per cent had reactions following the introduction of insulin. An explanation for the increase is not apparent. The possibility exists that because more people have had insulin, sensitization may have occurred because of this but there is an increased incidence of hypersensitiveness in patients who have never had insulin. There has been no apparent change in the quality of insulin but there appears to be a variability in behavior with different lots of the preparation. The authors detailed the type of reaction in their last 100 cases in which this happened. Eighty-four showed a mild allergic local reaction characterized by immediate stinging, burning pain at the site of injection followed an hour or two later by swelling of the tissues and redness of the skin, associated with burning and itching, and disappearing from 1 to 3 days. Twelve of the group had a somewhat more severe reaction as shown by intense inflammatory change in the injected skin and subcutaneous tissue, at times associated with fever and malaise, the local lesion not subsiding for at least a week. A general allergic reaction was seen in 4 cases manifested by subcutaneous, circulatory, and at times, gastrointestinal symptoms and in one instance a generalized dermatitis. The severe symptoms come on immediately but the signs of circulatory collapse subside within an hour or two. These severe general reactions occur only in patients who have had insulin and then have ceased. There is not very much question but that these reactions represent true hypersensitiveness to insulin, proven in part by cutaneous tests which were strongly positive. The importance of the skin test must be discounted to a certain extent in that positive reactions occur at times in individuals who show no hypersensitiveness. In these 100 patients desensitization was spontaneous in 8. There were 64 instances in which relief followed change in the type of insulin. In 22 instances in which nothing could be done to relieve the symptoms, fortunately it was possible to stop insulin after the diet had become satisfactorily adjusted but in 6 cases of severe diabetes nothing that was tried had any effect on the reaction of the patient. It was necessary to continue with the insulin. In none of these patients was there any interference by the hypersensitivity with the effect of insulin on the diabetes. Such cases have been reported, an example of which is quoted by the authors in which 600 to 700 units of insulin were required daily, and another instance in which apparently the injection of insulin interfered with the action of the insulin secreted by that particular individual's pancreas. The authors found no such cases in their series. They raise the question of how such cases should be treated and suggest

the following policy: Control the diabetes by diet if possible. If this cannot be done insulin must be employed as the danger from a diabetic death is greater than from an allergic death. Change the preparation. If there is still an allergic reaction attempt to desensitize by minimum dosage and increase gradually. Local measures such as soothing lotions are not much help nor is mixing the insulin with a local anesthetic, nor varying its reaction. Calcium has been of no value. In reviewing this interesting paper the thought arises as to the danger of administering insulin intravenously to those patients who come into general hospitals in coma who previously had insulin and discontinued it. This is an extremely common occurrence in large general charity hospitals and it is quite possible that insulin may have caused death in a certain number of instances as a result of anaphylactic reaction rather than death from diabetic coma. It might seem that a policy of caution should be followed in administering insulin intravenously to patients who have previously had this specific preparation and who have discontinued it, ultimately slipping into coma.

SURGERY

UNDER THE CHARGE OF
T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

The Colon as a Site of Focal Infection in Nonspecific Urethritis.—REDEVILLE (*Urol. and Cutan. Rev.*, 1931, 25, 620) says that the experimentation has proved that bacteria from the colon can pass through its walls into the lymphatic and blood stream through the kidneys and produce a nonspecific urethritis. The verumontanum is like a weather gauge indicating various conditions in the pelvis and becoming especially hyperemic in a condition of colon stasis and constipation. Men past middle life with a history of no specific infection, who are heavy eaters, who take no regular exercise and with a blood pressure usually above normal, may be harboring a condition of colon stasis in which cases there is a tendency to low grade generalized infection from the colon of the pelvic organs and especially the prostate. Some of the newer effective methods of treatment of nonspecific as well as specific cases are iodized autoserum, intramuscular, soluble iodine intravenously and the local and general diathermy fever heat treatments.

The Incidence of Gall Stones and Gall Bladder Disease.—CRUMP (*Surg., Gynec. and Obst.*, 1931, 53, 447) states that in the study of material from 1000 routine autopsies at the City Hospital in Vienna, the following facts were brought to light: 450 were males while 550 were females. Eighty-seven and one-tenth per cent of the individuals were over 30 and 77.9 per cent were over 50 years of age. Gall stones were present in 32.5 per cent of the cases. These were present in 37.8 per cent of the females and 26.2 per cent of the males. Twenty-five per cent of the individuals were affected after the fourth decade and 50 per cent after the seventh decade of life. Inflammatory or common gall stones

made up 73 per cent of the stone cases. Cholecystopathy occurred in 59.6 per cent of all cases and affected males in 58.4 per cent and females in 60.2 per cent. With the advance of the decades the case incidence increased from 20 per cent in the first age group to 77.6 per cent in the eighth decade of life. Chronic pericholecystitis was the most frequent pathologic condition and chronic cholecystitis was next in frequency. Primary carcinoma of the biliary tract occurred in 26 instances—7 males, 19 females—in which stones were present in all but 4 cases. In 2 cases the growths were primary in the ducts. Cholesterosis of the gall bladder was present in 36.8 per cent of all cases. Males were affected in 35.8 per cent and females in 37.7 per cent of the cases. This condition was very frequent in the early decades and maintained a more or less constant average throughout the age groups. Pathologic conditions were present in 41.3 per cent of all cases. There was an increase in incidence of disease with the advance of the decades. The most frequent finding was dilated ducts in 50.8 per cent and next frequent a lacerated papilla of Vater in 47.7 per cent of the abnormal findings. Gall stones were found in the bile ducts in 78 cases, which is 24 per cent of the cases with cholelithiasis. This finding was not affected by the age of the individual so that any patient with gall stones has one chance in four of having stones in the bile ducts.

Malignant Changes Occurring in Benign Giant-cell Tumors of Bone.

—SIMONS (*Surg., Gynec. and Obst.*, 1931, 53, 469) says that amputation cures 100 per cent of the cases of giant cell tumor. Resection or complete excision can be expected to cure 100 per cent of the cases. The only patient dying of the disease treated in this manner had no local recurrence, which is all that can be expected of the operation and there is also some doubt as to the correct diagnosis in this case. Curetting cures 63 per cent of the cases. Combined with other treatment, as radiation, 72 per cent; radiation treatment alone cures 75 per cent of the cases. Treatment by Coley's toxin cured 42 per cent of the cases. Of the cases of accepted benign giant-cell tumor treated conservatively, 7.5 per cent died, presumably of metastases. In 3 cases in which it was possible to compare microscopic sections of the tumor first treated with that causing death, the character of the growth had changed from benign to malignant. There is no proved instance in the cases of giant-cell tumors in the Registry of Bone Sarcoma registered before 1925 of a tumor of this type causing death from metastases. There is definite evidence, however, that a benign giant-cell tumor may change its character and become an osteogenic sarcoma causing death. Uncontestable data are difficult to obtain but this change is known to have occurred in 3 cases in this series, 3.7 per cent.

Retroperitoneal Tumors.—COHN (*Arch. Surg.*, 1931, 23, 655) claims that retroperitoneal masses may be present and yet remain undetectable during life by any available diagnostic methods. The Roentgen evidence of extrinsic obstructive intestinal phenomena is interesting and diagnostic when present, but the absence of such a sign is by no means acceptable as evidence that a retroperitoneal growth does not exist. Retroperitoneal tumors sometimes move with respiration, thus making it difficult if the mass is on the left side to eliminate splenomegalia.

The symptoms caused by a retroperitoneal growth are dependent on the location of the growth. Proximity to the celiac plexus causes digestive phenomena, whereas growths even of larger size in other locations may not cause digestive disturbances. Digestive disturbances are not diagnostic as they are present in so many conditions other than retroperitoneal tumors. Anemia is present in many cases of retroperitoneal growths but is not to be relied on as a diagnostic phenomenon. Anemic and digestive disturbances may mislead one to treat the patient for an entirely different condition. Edema of extremities and ascites are present when the growth is large and when it is so situated as to interfere with the venous return. A growth situated on the right side readily produces edema, whereas a large growth on the left side may not be associated with edema of the lower extremities or ascites. Retroperitoneal masses may be associated with chylous ascites and chylous pleural effusions. Retroperitoneal sarcomas may be primary and productive of metastases, whereas other retroperitoneal sarcomas may be secondary growths. When searching for the primary cause of retroperitoneal metastases, teratoma of the testicle must not be overlooked as a possible source.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

The Action of Digitalis on the T Wave of the Electrocardiogram.—Recently the inversion or flattening of the *T* wave of the electrocardiogram commonly accepted by American authors as being a fairly constant manifestation of the action of digitalis has been brought into question, particularly in Europe. COELHO (*Arch. d. mal. du cœur*, 1931, 24, 746) reviews the more important literature on the subject and presents the results of his own carefully controlled observations upon man. He employed digitan (digipuratum) in varying doses in a group of 22 patients with cardiac disease. Whereas others have found inversion of the *T* wave to occur in as much as 90 per cent of patients receiving adequate doses of digitalis, the author obtained inversion in only 18 per cent of his cases. He also found that the inversion bore no necessary relation to the total dose of digitalis taken, the phenomenon occurring as well with moderate doses as with those which were extremely large. He calls attention to the fact that inversion of the *T* wave is a fairly frequent occurrence in the presence of chronic myocardial disease, myocardial infarction and occasionally in apparently normal hearts due to some undetermined factor. From his studies he believes that

this alteration in the electrocardiogram cannot be regarded as a characteristic manifestation of digitalis action and, furthermore, that it is not a safe guide for the control of digitalis administration. He suggests that in those cases in which it appears it is due to certain conditions associated with chronic myocardial disease which may be brought to light as a result of digitalis action rather than being due primarily to the actions of the drug itself.

The Treatment of Agranulocytosis With Roentgen Ray Irradiation and Blood Transfusion.—Opinions regarding the effect of Roentgen ray irradiation of the long bones in agranulocytosis are somewhat contradictory. HARTWICH (*Klin. Wchnschr.*, 1932, 11, 104) used repeated Roentgen ray treatment in 3 cases of agranulocytosis. The beneficial effect of the treatment in these cases manifested itself in a temporary rise in the white cell content of the blood. Definite permanent improvement, contrary to the experience of Friedemann, was not observed. There are several reports in the literature which claim that blood transfusion is beneficial in this condition. Blood transfusion was used in 6 patients. In each instance the author claims there was a prompt clinical improvement. The temperature subsided with crisis or with lysis, and at times there appeared a most astonishing improvement in the necrotizing process of the throat. There was also an increase in the white cell count. This, however, was not always permanent. The author observed repeatedly that the general clinical improvement, the fall in temperature and the healing of the ulcerated mouth lesions were quite independent of the number of white blood cells. The author advocates the more frequent use of blood transfusion in the treatment of agranulocytosis.

The Treatment of Ulcus Cruris.—Among the numerous therapeutic agents used in the treatment of chronic ulcers of the lower extremities, KUN (*Münch. med. Wchnschr.*, Jan. 1, 1932, vol. 26) claims that "lyssia salve" is most effective. The composition of this salve is as follows: Zinc oxidat. amyl., 15 gm. āā; vassel fl., 35 gm.; naftalan, 16 gm., balsam Peruv., 6 gm.; chinolin sulph., 0.5 gm.; ichthyol, 1 gm.; extr. hamam. fl., 3 gm.; oleum cacao, 3 gm.; bism. oxyiodogall., 1 gm.; adeps lanæ ad. 100 gm. The ulcer is cleaned with benzine and covered with the salve in the morning. Within a day or two there is evidence of healing and within a short period granulation tissue fills in the ulcer. In ambulatory patients a bandage is applied following the application of the salve and removed 4 to 5 days later.

The Beneficial Effect of Calomel in Rheumatic Endocarditis and Pancarditis.—It is often not appreciated that calomel was used as a diuretic as early as the eighteenth century. MacKenzie has pointed out again that certain cardiac patients who do not respond to digitalis will show diuresis after the administration of calomel. PAUL and BABATZ (*Münch. med. Wchnschr.*, January 1, 1932, vol. 25) administered repeated doses of calomel in amounts of 0.2 to 0.3 gm. (3 to 5 grains) to patients who were suffering from repeated attacks of fever, valvular damage, cardiac enlargement, congestive failure of the circulation and anemia. The authors claim that in every case there was

subjective and objective improvement. They do not offer any explanation for the mechanism of action of calomel. In order to avoid nephritis the water balance was carefully followed. In the presence of casts in the urine calomel was not administered. The bowels were kept open before its administration. Under these conditions no kidney damage was observed. It is claimed that similar improvement was not observed after salyrgen or after mercurial preparations combined with proteins.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Mechanism of Hemophilia in Infancy and in Childhood.—KUGELMASS (*Am. J. Dis. Child.*, 1932, 44, 50) feels that criteria necessary and sufficient for the diagnosis have been formulated on the basis of experimental and clinical studies. It has been shown by a study of the constituents involved in blood coagulation that the hemophilic deficiency occurs in the primary stage of the blood-clotting mechanism. Hemophilic blood shows a strikingly low prothrombin content compensated by a correspondingly high antithrombin content. The platelets are normal in number but are physiologically defective, having a slow rate of disintegration. Hemophilic blood is characterized by a blood-clotting index that is less than one-tenth of normal. The index constitutes the ratio of the concentration of the substances tending to clot over those tending to favor bleeding. The normal index of clotting function is 0.5, whereas the hemophilic clotting index is less than 0.05. This very low index of blood-clotting is diagnostic of hemophilia. The index of blood-clotting function shows a great increase after transfusion, but the improved index last for only 48 hours. Transfusion does not alter the clotting function of blood in hemophilic subjects with manifestations in the joints. Dietary protein, lipids, vitamins and minerals do not alter the deficient blood-clotting function in hemophilia. Hemophilic individuals show the absence of the female sex hormone in their tissues normally present in males. Ovarian therapy, theelin and other products of the female generative organs injected into the hemophilic subject produce no change in the clotting mechanism evaluated quantitatively. Serum injected or applied locally is not effective in controlling hemorrhage in hemophilia, unless it is fresh and rich in thrombin. Nonhemophilic bleeders respond readily to any serum and to dietary protein therapy.

Iron in the Liver and in the Spleen After Destruction of Blood and Transfusions.—GLADSTONE (*Am. J. Dis. Child.*, 1932, 44, 81) examined a series of livers of fetuses and infants obtained at autopsies. He studied these microscopically and chemically to determine the variations in the amounts of iron present and the factors on which such variations depended. There was no evidence microscopically or chemically of large or progressive depositions of iron in the liver during the last 4 months of intrauterine life. Exclusive of iron as hemoglobin, the entire liver

of the mature new-born infant contains on the average about 32 mg. of iron. The largest amounts of iron were found in the liver from 1 to 10 weeks after birth, and these were believed to depend on postnatal intravascular destruction of blood. Hemosiderosis of the liver may also result from hemorrhages into the tissues or cavities of the body of the fetus or infant, and during fetal life it may result from similar hemorrhages in the mother, the liberated iron reaching the fetus through the placenta. Hemosiderosis of the spleen and the liver follows transfusion of blood. The amount of iron found in the liver is influenced by the size and the frequency of the transfusions. The appropriation and utilization of transfused blood was studied. It seems that in human beings at least part of the transfused blood is quickly phagocytosed. The red cells are physically disintegrated and chemically digested within the phagocytes, and the products are liberated into the blood stream. Among these products are bilirubin and iron derived from the hemo portion of the hemoglobin, and the poorly known but extremely important derivatives of the globin portion of the molecule. These studies indicate that in large amounts iron as well as bilirubin is taken up from the blood stream by the hepatic cells. It has been demonstrated also that the kidney removes large quantities of urobilin under these circumstances. The kidney has the power also of taking up iron from the blood stream after extensive destruction of blood, and this iron may be found in the urine.

The Effects of Parathormone and Ammonium Chlorid on Bones of Rabbits.—JAFKE, BODANSKY and BLAIR (*J. Exp. Med.*, 1932, 55, 695) found that a very large single dose of parathyroid extract produced rapid and extensive decalcification of the bones of a young rabbit. Gradually increased doses of the extract failed to produce significant changes in the young and fully grown adult rabbits. Ammonium chlorid, administered by the stomach tube, was without effect on the bones when given to rabbits treated with the extract or to otherwise untreated rabbits. Calcium lactate did not promote the appearance of signs of overdosage of parathyroid extract in rabbits during treatment, nor were metastatic calcifications observed in the soft tissues after termination of the experiment. The rabbit is highly resistant to the decalcifying effects of gradually increased doses of parathyroid extract, and is therefore not satisfactory material for experimental studies of bone changes of chronic hyperparathyroidism. The appearance of actively transforming bones of a young growing rabbit, particularly at the site of rapid growth, is not to be confused with the more severe fibrous processes produced by parathyroid extract in guinea pigs, dogs and rats.

Progress in the Nutrition of Infants.—DURAND (*J. Am. Med. Assn.*, 1932, 99, 275) summarizes the essential points of the problem of infant feeding. The casein curd of cow's milk must be modified. To do this efficiently boiling and acidification are employed. The question of buffer substance is not of the greatest importance. The use of accessory food factors not only prevents rickets, its resultant deformities and the more fatal tetany, with scurvy, xerophthalmia and the other forms of avitaminoses, but also incidentally improves the resistance of the infant to infection. It is recognized that hunger is the greatest danger of the

infant and the younger child the greater is the danger. The use of the cereal waters and very weak formulæ weaken the baby and render it more liable to infections. The early broadening of the diet is now generally accepted. In general the best guide to the optimal proportions is that of breast milk in which protein, fat and carbohydrate are found in the percentages of 1, 3.5 and 7. There is a growing tendency to reduce the amount of milk in infant feeding. Limitation of the total quantity of fluid must be considered. Except during periods of excessive heat or during fever or watery diarrhea, the infant does well on one-fifth of its body weight of fluid daily during the first weeks, one-seventh at 6 months, and one-eighth up to the first year. If fluids are kept near this level, less vomiting occurs, the bottle is more readily emptied, the bed and clothing are not so constantly water-soaked, the insulation against changes in surrounding temperature is consequently better and the skin is less irritated.

Celiac Disease.—HAAS (*J. Am. Med. Assn.*, 1932, 99, 448) states that there are a constitutional tendency to the disease and a characteristic intestinal flora. There appear to be a faulty absorption and utilization of carbohydrates and fats. The fats are of secondary importance, for if strict attention is paid to the carbohydrate intake, tolerance of fats follows. A flat blood sugar curve is probably pathognomonic of active celiac disease. The successful treatment of celiac disease requires a high protein diet, of which the basis is protein milk, to which is added carbohydrate in the form of ripe banana powder and ripe banana, although other fruits and some vegetables are tolerated in some degree. The author claims that no nutritional relapses occur with this diet. A relapse not due to an acute infection is always due to the introduction of some carbohydrate other than that of banana, or rarely due to some intolerable fat. The banana contains all vitamins except vitamin D. It hydrolyzes starch and transforms the intestinal flora and produces starch-free alkaline stools. Vitamin D must be used as the concentrate viosterol and not as cod liver oil, and for the anemia accompanying celiac disease some form of iron must be given. The prognosis in cases of celiac disease under this treatment is excellent, and the patients attain full stature and are capable of using a normal diet.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Reactions Following the Administration of the Arsphenamins and Methods of Prevention.—IRELAND (*Am. J. Syph.*, 1932, 16, 22) reviews the record of 2100 patients receiving arsphenamins for the treatment of syphilis and reaches the following conclusions as to the incidence

and type of reactions noted: 11.2 per cent of the patients showed various symptoms of intolerance to the arsphenamins, the most common type being of gastrointestinal origin. Old arsphenamin was much more reaction-producing than neoarsphenamin. Of the reactions observed, 72 per cent occurred early in the course of treatment between the first and tenth injections although no particular type of syphilitic involvement appeared to predispose to intolerance. The probability of reaction appeared to be twice as great in females as in males. The author believes that reactions can be very largely controlled by the complete physical appraisal of the patient before the institution of treatment, the introductory use of iodid and mercury in patients with syphilitic visceral involvement, the recognition of the importance of conservative dosage, slow administration and adequate dilution in preventing reactions, and finally such adjuncts as the preliminary injection of atropin or adrenalin, ephedrin by mouth, calcium gluconate intramuscularly and vehicles other than distilled water. The author's review of the literature reveals a very diversified list of reactions but he points out that the number of severe or fatal reactions is low when the large number of patients under treatment is considered.

Unusual Clinical Manifestations Following Intravenous Administrations of Gold Compounds.—THRONE, KINGSBURY and MYERS (*Arch. Dermat. and Syphilol.*, 1932, 25, 494), on the basis of their own experience as well as that recorded in the literature, review the wide range of toxic reactions encountered after the intravenous use of gold compounds in lupus erythematosus, tuberculosis cutis and the tuberculids. These reactions have already been summarized in the review of Driver and Weller's article, which appeared in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES for October, 1931. The present authors offer the following suggestions to prevent the untoward effects of gold administration: (1) The patient should be examined for focal infections which, if found, should be removed prior to the institution of gold therapy. (2) A preliminary analysis of the blood should be made to determine the possible presence of a high sugar and low chlorid content which demands a preliminary course of injections of sodium thiosulphate. In cases showing a high blood sugar content not associated with pancreatic deficiency or metallic retention, the doses of the gold compound should be comparatively small. Patients with definite diabetes, however, seem to tolerate treatment with gold preparations. (3) The first sign of intolerance, as manifested by dryness of the mouth and pruritus, is an indication for discontinuance of the gold compound and the use of sodium thiosulphate. In the authors' experience, these symptoms are invariably accompanied by an increase of the blood sugar, a decrease in the chlorids and frequently by a marked decrease in the urea nitrogen. (4) Chemical examination of the blood at weekly intervals for the foregoing changes may enable one to foresee an intolerance to gold which can be prevented by proper eliminative treatment. (5) The initial dose of a gold compound should be small, not exceeding 25 mg. This dose can be increased if well borne and relatively non-effective, but the dose should be kept low if the clinical response is satisfactory. (6) Positive contraindications for gold therapy are marked hepatic and renal disturbances, pregnancy, lupus erythematosus disseminatus acutus, and elevation of temperature.

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Surgery of Pelvic Sympathetic Nerves.—The surgery of the sympathetic nervous system has received an unusual amount of attention in recent years, and from the reports in the literature the results of many of these operations have been well worth while. The gynecologists must now interest themselves in this subject, at least from the theoretical standpoint, since the work of FONTAINE and HERRMANN (*Surg., Gynec. and Obst.*, 1932, 54, 133) of Leriche's Clinic in Strasbourg indicates that there may be a fertile field for this type of surgery in relieving certain pelvic disorders in women. The latter investigators believe that the hypogastric plexuses carry the important pathways of sensation from the internal genital organs to the medullary centers and that the section of the superior hypogastric plexus (presacral nerve) above the hypogastric ganglion is a safe, simple and efficacious way of interrupting these pathways in the treatment of the functional type of dysmenorrhea as well as a method of relieving other forms of severe pelvic pain. The cases in which pelvic sympathectomy is indicated, according to their views, can be divided into three main groups: Group A: Those cases in which no organic lesion of the genital organs can be found to account for the pelvic pain, *i. e.*, functional dysmenorrhea. Group B: Those cases with slight pathologic processes in the pelvis which do not react favorably to ordinary gynecologic treatment, *i. e.*, sclerocystic degeneration of the ovaries or persistent pelvic pain following some previous operation. Group C: Those cases in which the pathologic lesion is known but which has been found to be too extensive for surgical removal, *i. e.*, inoperable neoplasms in the pelvis giving rise to severe pain. They have performed resection of the superior hypogastric plexus for the relief of severe pelvic pain in 22 patients. Six of the patients have failed to return for follow-up examination, but at the time of discharge from the hospital they were completely relieved of their pain. One patient died on the second postoperative day, while 13 of the 15 patients that have been followed have been relieved of all pelvic and abdominal pain for periods of time up to 4 years. Two patients have had only slight or no benefit from the operation. The technique of the operation as they describe it is quite simple. With the patient in the Trendelenburg position, the small intestines and colon are packed upward toward the diaphragm and the rectosigmoid is retracted toward the left. The promontory of the sacrum and the two common iliac arteries are then located. The posterior parietal peritoneum is then incised at a point just above the promontory of the

sacrum and directly in the midline. Immediately beneath the peritoneum and anterior to the midsacral artery will be found the nervous filaments which constitute the superior hypogastric plexus. In very thin women these fibers can be seen through the peritoneum, while in obese women the plexus is usually embedded in adipose tissue. If the mesosigmoid is short, care must be taken not to injure the inferior mesenteric vessels. Frequently several nerve fibers are densely adherent to the right iliac vein. After all the filaments have been isolated, a segment, at least 1 inch long, should be resected from each main nerve fiber in order to prevent any possible regeneration. The posterior peritoneum is then closed by a continuous catgut suture. While it is appreciated that the Strasbourg school is perhaps unduly enthusiastic about the surgery of the sympathetic nervous system, it would seem that this procedure might be well worth while trying in some of the patients who have such intense dysmenorrhea and have been unrelieved by all other treatment except hysterectomy. (Especially indicated in certain carefully selected cases of incurable cancer in whom other methods fail to relieve pain.—C. C. N.)

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

The Influence of Pregnancy on the Visual Field.—JOHNS (*Am. J. Ophthalm.*, 1930, 13, 956) reports the results of her examinations of the fields of vision of 29 young women in the course of essentially normal uncomplicated pregnancies. Only 1 of these patients showed any definite evidences of pituitary dysfunction. With one possible exception, none of them showed any diagnostic changes in the preoperative and postoperative rays of the sella turcica. The visual fields were studied at rather frequent intervals in the prepartum period of observation and were checked postpartum. In about 80 per cent of the patients a definite tendency to concentric contraction of the form and color fields was found. This tendency was most marked in the last four weeks of pregnancy and increased up to the time of delivery. The fields tended to return to normal after delivery. In 20 of the 29 patients the blind spots were enlarged. A characteristic pituitary type of field was not found in any case. The author believes that these field changes are secondary to a general reduction of retinal vitality which is part of the general lowered vitality of the pregnant state and that they are not due to enlargement of, or vascular changes in, the pituitary gland.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

A Study Concerning the Incidence of Streptococcus Epidemicus.—The occurrence of septic sore throat and of carriers of *Streptococcus epidemicus* during interepidemic periods has become a matter of importance. Inasmuch as southern California has never had an epidemic of septic sore throat, BONYNGE (*Proc. Soc. Exper. Biol. and Med.*, 1931, 28, 991) over a period of 4 months conducted a series of *Streptococcus epidemicus* among certain groups of persons in Los Angeles. From the throat swabs of 250 apparently healthy employees, *Streptococcus epidemicus* was recovered from 7 individuals, none of whom had had septic sore throat and all of whom had hypertrophied tonsils—a percentage of 2.8 for the “carrier group.” Of 66 persons presenting themselves for removal of hypertrophic tonsils, *Streptococcus epidemicus* was isolated in 6 (9 per cent). In 2 children otitis media and subsequent mastoiditis was found to be of *Streptococcus epidemicus* origin. In all, 18 strains of *Streptococcus epidemicus* were recovered; 5 from persons suffering from acute infections and 13 from human carriers. The author’s results are not widely variant from those obtained in Chicago by Pilot and Davis (*J. Infect. Dis.*, 1930, 47, 503).

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,
AND
CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Roentgenologic Study of Intrathoracic Lymphoblastoma.—Sixty-seven cases of intrathoracic lymphoblastoma, comprising 40 cases of Hodgkin’s disease, 17 of lymphosarcoma and 10 of leukemia were studied by KIRKLIN and HEFKE (*Am. J. Roent. Ray and Rad. Therap.*, 1931, 26, 681). In the opinion of the writers, roentgenologic examination of the thorax in cases of Hodgkin’s disease, lymphosarcoma and leukemia does not permit a precise diagnosis of any one of these diseases. They must be considered as one group which might be called either lymphoblastoma or malignant lymphoma. Demonstrable roentgenologic manifestations in the thorax may be expected in about 50 per cent of the cases of Hodgkin’s disease, and in about 20 per cent of the cases of lymphosarcoma or of leukemia. In the series reported, enlargement of the mediastinal and hilar nodes was the most common manifestation. Involvement of the lungs, either of the infiltrative or metastatic type was found in 30 per cent of the cases of Hodgkin’s disease, in about 23 per cent of the cases of lymphosarcoma and in 40 per cent of the cases of leukemia whenever intrathoracic involvement was demonstrable.

Roentgen Ray Pelvimetry—A Simplified Stereoroentgenographic Method.—A method of pelvimetry by stereoroentgenography is described in considerable detail, with illustrations and explanations of each of the three stages, by HODGES and LEDOUX (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 83). No special professional ability is required of the person making the films, and the apparatus may be used not only for pelvimetry but for practically any type of Roentgen examination.

Hepatography and Lienography Following the Injection of Thorium Dioxid (Thorotrast).—In order to demonstrate the shadow of the liver and spleen roentgenologically, STEWART, EINHORN and ILLICK (*Am. J. Roent. and Rad. Therap.*, 1932, 27, 53) have tried the injection of thorotrast in 8 cases. The drug is supplied in ampules, each containing 3 gm. of thorium dioxid suspended in 12 cc. of water. The mixture was injected intravenously and very slowly, and a second ampule, or more, was given next day or the second day after. The material was well tolerated up to an hour after injection in all cases. Five had no definite after effects. Three had vomiting attacks for several days after the injection and 2 patients had hemorrhages. Subsequently 7 of the 8 patients died, but no death was directly attributable to the drug. No increase in density of the liver and spleen occurred until after 24 hours, and the maximum density was reached in 1 or 2 weeks. A dense shadow of the liver was obtained in all patients except 1 who died shortly after. In 1 case the shadow of the liver was mottled; the diagnosis of malignant disease was confirmed at operation. In 7 cases the spleen was also demonstrable; the shadow varied in intensity and in a few instances was quite dense.

Radium as an Adjunct to Surgery in the Treatment of Carcinoma of the Fundus of the Uterus.—BOWING and FRICKE (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 738) relate their experience with 189 cases of carcinoma of the fundus, 172 of which were traced. Of the 189 patients, 87 were treated by operation and irradiation, and 102 were treated by irradiation only. The late results in a few favorable cases in which irradiation alone was used compare favorably with the results obtained by operation alone. The authors regard irradiation as an invaluable adjunct to surgery. Irradiation alone yields high returns in palliation but poor remote results, mainly because the majority of lesions are too advanced to permit adequate treatment.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO.

Regenerative Possibilities of the Central Nervous System.—GERARD and GRINKER (*Arch. Neurol. and Psychiat.*, 1931, 26, 469) feel that there is "good evidence of spinal regeneration in amphibia and other

lower vertebrates" as well as the reported evidence of regeneration of the optic nerve in adult rats and spinal regeneration in birds and mammals in literature. They present a series of experiments on newborn rats and rat fetuses *in utero* in which the spinal cords were transected by a single clean cut with a cataract knife, and subsequently studied histologically. "Many experiments yielded negative or no results because the animals died or the true spinal column became displaced. Several rats operated on at birth, however, gave evidence of a gradual return of function. One animal, studied with special care, which showed evidence of a complete section at the time of operation, was entirely paralyzed and anesthetized below the lesion for 2 weeks, while in a subsequent 3 weeks the recovery of sensation and voluntary sensation and motion was practically complete. The spinal cord of this animal showed no evidence of a lesion. Several rats operated on *in utero* were born from 5 days to 1 week later with the sense of pain, voluntary motion or both present in the hind quarters. The spinal cords showed partial lesions or none at all." The authors consider the possibilities of the growth of nerve fibers into and across a lesion after complete or partial transection of the spinal cord is definitely established.

The Cerebral Lesions in Purulent Meningitis.—WERTHAM (*Arch. Neurol. and Psychiat.*, 1931, 26, 549) presents a histologic study of the cerebral parenchyma of 24 cases of purulent meningitis. Apart from the changes of an encephalitic and toxic degenerative type, he noted other lesions of the nervous parenchyma. These lesions were chiefly in the cortex, but subcortical structures such as the basal ganglia were also affected, especially in children. He found for most of the lesions a circulatory basis as the chief factor in their production with toxic factors playing a subordinate part. If a full-fledged encephalitis supervenes the infection does not progress from the outer and ventricular surfaces, but the encephalitis attacks the central parts of the substance of the brain like an independent process. Therapeutic procedures directed toward relief of the circulatory system, the author feels, are necessary in purulent meningitis.

The Choroid Plexus as a Dialyzing Membrane: I. Observations in Experimental Hydrocephalus.—HOEN (*Arch. Neurol. and Psychiat.*, 1931, 26, 496) presents a study of experimental hydrocephalus produced in 18 days by obstruction of the aqueduct of Sylvius. The experimental work involved: (1) Alterations in the volume of the spinal fluid, and (2) alterations in its salt content. "The former caused only transient changes in ventricular pressure, whereas within the time limit of the experiment the latter caused permanent changes." This observation is possibly of clinical importance in cases which require spinular ventricular tapping for relief of pressure.

Family Periodic Paralysis: Report of a Case.—ZABRISKIE and McDONALD (*Arch. Neurol. and Psychiat.*, 1932, 27, 220) present the case of a man, aged 23 years, who had suffered intermittent attacks of flaccid paralysis since the age of about 7 years. The onset of the attacks was nearly always at night, beginning with a numb feeling in the back of the neck, followed by weakness of the legs, then of the trunk.

then of the arms, and finally of the muscles of the neck. In severe attacks there was virtually complete paralysis of all the muscle groups mentioned. There was no involvement of the cranial nerves. The paralysis was flaccid, with decrease or loss of the deep reflexes. The attacks lasted from 2 to 24 hours. There was considerable sweating at the beginning and end of an attack. A systolic murmur, with enlargement of the heart to the left, occurred in several of the more complete attacks. Electrocardiograms gave negative results. All laboratory studies were negative. A partial attack, *viz.*, that of one forearm, could be induced by local cooling. The patient's mother had suffered from the same disease and died during an attack of paralysis at the age of 23 years.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Malignancy in the Lung, Including 8 Primary Carcinomas With Autopsy Findings.—Eighty-one cases of malignant tumors of the lung have been reviewed by MOSES (*Am. J. Int. Med.*, 1931, 5, 765). Of these, 8 have proven primary carcinomata of lung at autopsy. Thirty-five cases were considered clinically as primary carcinoma of lung, post-mortem examination not having been made. Secondary carcinoma of lung occurred in 20 cases of this series, metastatic lymphosarcoma in 10 and metastatic sarcoma in 6. One case of secondary hypernephroma and 1 of teratoma were also encountered. Of carcinomata that metastasize to lungs, breast and kidney tumors are considered the most important. Histologically three types of pulmonary carcinoma are recognized—those from bronchial epithelium, from bronchial mucous glands and from alveolar epithelium (bronchogenic or parenchymatous). Carcinoma from bronchial epithelium often causes bronchial obstruction but seldom a diffuse tumor of lung. Those from glands usually arise in the larger bronchi while those from alveolar epithelium produce infiltrating and often rapidly spreading tumor masses involving large areas and frequently resembling organizing pneumonia. The commonest symptoms encountered were cough, with or without sputum, hemoptysis, dyspnea, pain either constant or paroxysmal, cyanosis, weakness and emaciation. The author calls attention to the fact that the occurrence of an unexplained pleurisy, especially a pleurisy with an effusion, in a patient in middle or later life should suggest the presence of a new growth in lung or mediastinum.

Enzoötic Hepatitis or Rift Valley Fever.—DAUBNEY and HUDSON (*J. Path. and Bacteriol.*, 1931, 34, 545) describe a new virus disease which made its appearance as an epizootic of serious proportions in a large colony of sheep in the Rift Valley, Kenya Colony, East Africa.

The outbreak was carefully investigated, both as to pathology and bacteriology. Sheep, cattle, goats and man are susceptible. The mortality is over 95 per cent in very young lambs, but is low in adult sheep and cows and practically *nil* in man. There is a marked tendency for pregnant ewes and cows to abort during the course of the disease. In man there is but a slight transient fever often accompanied by joint pains. The characteristic lesion found in animals dead of the disease is a liver necrosis which is strikingly similar to that of yellow fever. (KLOTZ and BELT, *Am. J. Path.*, 1930.) Both cytoplasmic and nuclear "inclusion bodies" occur in the affected liver cells. The virus is a filter passer and there is evidence to show that it is transmitted by a mosquito (*Tæniorhynchus brevipalpis*). It is suggested that the disease falls into the same group as yellow fever and dengue. (Editorial, *Lancet*, October 3, 1931, p. 751.)

Melanosis Mucosæ Appendicis Vermiformis.—LILLIE (*Am. J. Path.*, 1931, 7, 701) reports melanotic pigmentation of varying degrees present in 266 out of 750 human appendices examined. The condition is of a nature similar to melanosis coli described by PICK (*Berl. klin. Wchnschr.*, 1911, vol. 48). The pigment lies in cells of a macrophage or fibroblastic type immediately beneath the mucosal epithelium. The pigmentation increases with age but is unrelated to race, sex or occupation. It is infrequently demonstrable in appendices which are the seat of active inflammation. Dilatation or atony of the appendiceal wall is correlated with an increased frequency and intensity of the pigmentation.

A Case of Myeloma With Unusual Amyloid Deposition.—PAIGE (*Am. J. Path.*, 1931, 7, 691) presents a case of multiple myelomata in which there occurred tumorlike masses of amyloid in the muscles about the shoulder girdle. There was also a heavy deposition in nearly all organs and tissues of the body except the liver. All the usual staining reactions for amyloid were positive. Bence-Jones protein was present in the urine. The author is able to find in the literature reports of 3 other cases of multiple myelomata accompanied by amyloidosis. He favors Well's suggestion that the deposit may be a "consolidation of the Bence-Jones protein."

Etiology in Influenza.—LISTON (*Glasgow Med. J.*, 1930, 113, 64) believes that Pfeiffer's bacillus is not a normal saprophyte of the air passages and that the abandonment of this organism as the causal agent in the disease by many bacteriologists is due to failure to use suitable media for isolations and to confusing microorganisms found in normal throats with *Bacillus influenzae* proper. While numerous reports, in recent years, have described the almost constant finding of organisms culturally identical with *Bacillus influenzae* in the throats of normal individuals, it should be remembered that the identity of these has not been clearly proven as the only method at present available for identification of the hemoglobinophilic bacteria is their nutritional relationship to hemoglobin. The author states that he generally can distinguish members of this group from the true Pfeiffer bacillus by sugar fermentations. Should further study show that this is a reliable method of subdivision then considerable advance will have been made in our knowledge of these bacteria and their etiologic significance in influenza.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Oral Immunization Against Pneumococcus Types II and III and the Normal Variation in Resistance to These Types Among Rats.—Ross (*J. Exp. Med.*, 1931, 54, 875) found considerable variation in the resistance of different rats toward Type II pneumococcus. In general, older rats survive much greater doses than young ones, illustrating the acquisition of a natural partial immunity. The same is true for Type III but the immunity appears somewhat later in life and does not reach the same height. An active immunity can be created against Types II and III in rats by feeding the dead organisms or the Berkefeld filtrate of the bile salt-dissolved cells. This immunity resembles that obtained against Type I in several respects. *The Rôle of the Soluble Specific Substance in Oral Immunization Against Pneumococcus Type I.*—In further experiments (*Ibid.*, p. 899) it was found that feeding the purified soluble specific substance of Type I pneumococcus protects rats against an intraperitoneal injection of the virulent organism. This increased resistance resembles that obtained when the intact (dead) or dissolved bacteria are fed, as follows: (a) One feeding is sufficient; (b) the interval between the feeding and the appearance of the immunity is the same; (c) the duration is approximately the same; (d) when the immunity is exhausted it can be renewed by a new feeding; (e) the immunizing action is type specific. The differences between the effects of feeding the purified specific substance and the intact or dissolved organism to rats appear to be quantitative rather than qualitative, the proportion of animals protected and the height of the immunity being generally, though not always, less in the case of the former. In contrast to the immunizing action which the soluble specific substance possesses when administered to rats, feeding it to mice failed to protect them. Neither were mice definitely immunized by parenteral administration. A sodium glycocholate solution of pneumococcus Type I lost part of its immunizing activity on standing for 1 year. The failure to immunize mice and the loss of activity of the bile salt solution of pneumococcus, on standing, are discussed in terms of (a) the possible presence of a second cell constituent which is active by mouth and (b) a possible intramolecular change in the type-specific polysaccharid associated with a loss of immunizing action while retaining the precipitin reaction.

The Movements of Epidemic Meningitis, 1915-1930.—HEDRICH (*Pub. Health Rep.*, 1931, 46, 2709) discusses the subject in detail and presents the following summary: This paper reviews some of the general epidemiologic characteristics of epidemic meningitis, and the recent movements of the disease as to time and place: (1) The available

evidence indicates that during epidemics surprisingly large proportions of the population may at one time or another become infected with the meningococcus. Under highly congested conditions, as in army camps, it appears that practically the entire population may become infected once or oftener during epidemics. Probably far less than 1 per cent of such infections result in clinical attack, as annual attack rates in excess of 1 per 1000 population are rare. The case fatality, however, is heavy; approximately half of the reported cases died during the recent epidemic, in spite of fairly widespread use of serum. (2) Meningitis became increasingly prevalent in Europe shortly after the opening of the World War, and in the United States shortly after her entry, when mobilization began. The highest attack rates in England came in 1915, and in the United States in 1918. In 1928-1930 the disease was again epidemic in most part of the world. (3) The interval between the last two epidemic maxima was 11 years in the United States, and a few years longer in most European countries. The interepidemic interval is highly variable. It has oftenest been 6 to 12 years, but some areas have run as long as 25 years without epidemics. Massachusetts, for example, has had no appreciable epidemic since about 1905, and New York City only a minor one, namely, in 1928-1930. (4) Over broad areas, such as large groups of states, epidemics have appeared, not as sporadic explosions but as crests of rather smooth and systematic wave, the rise and declining phases of which have covered a period of 3 to 6 years or longer. Within smaller areas, such as individual cities, the movements of the disease have been less systematic. (5) Neither of the last two epidemics was synchronous in different parts of the United States, some regions having lagged 2 years behind others. The time rate of epidemic development within specific areas, and the rate of geographic movement are very much slower for meningitis than for influenza. (6) In the 1918 epidemic the reported attack rates were highest in the southern sections, probably due to the large number of military concentration camps; the Rocky Mountain states had the lowest rates. In the 1928 outbreak the southern states had the lowest and the mountain states the highest rates.

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ORIGINAL ARTICLES.

THE SOCIAL INCIDENCE OF RHEUMATIC HEART DISEASE.

A STATISTICAL STUDY IN YALE UNIVERSITY STUDENTS.

BY JOHN R. PAUL,

ASSISTANT PROFESSOR OF MEDICINE,

AND

P. A. LEDDY,

CLINICAL INSTRUCTOR IN MEDICINE,

NEW HAVEN, CONN.

(From the Departments of Internal Medicine, Yale Medical School, and University Health, Yale University.)

It has been tacitly accepted by many that rheumatic fever is a disease which finds its highest incidence among individuals living under poor hygienic conditions, and that these poor living conditions are generally an expression of limited economic means. Unfortunately, few statistical data exist in the United States on which to base this contention, although it would seem to be a point of considerable import. From England we have Miller's¹ statement that: "Although technically the rheumatic infection may not be a 'poverty-disease' in that its frequency does not seem to follow absolutely the variations in degree of poverty, yet nothing is more certain than that it is a disease of the poorer classes." Glover² also believes that: "No disease has a clearer cut 'social incidence' than acute rheumatism, which falls perhaps thirty times as frequently upon the poorer children of the industrial town, as upon the children of the well-to-do." Statistics³ to bear out the contention that rheumatic fever is a disease seen with great frequency

in hospital wards, as opposed to private pavilions and consulting practice, show that among 1000 children from the Outpatient Department of King's College Hospital, London, the incidence of those who showed evidence of acute rheumatism was 13.1 per cent, whereas among 700 children from private practice the incidence was only 0.7 per cent. Other British observations on the subject include those of Hutchison,⁴ who comments on the differences between the incidence of rheumatic fever in private practice and in hospital wards; of Coombs,⁵ that it is quite certainly a rare disease among the well-to-do; and of Campbell and Warner,⁶ who have the impression that the poorest are most commonly affected. The last statement, however, is qualified by some observers, reflecting Miller's views already quoted, that the disease tends to be more frequent among children of the decent poor, than among the squalid.⁷

Evidence which also bears on the factor of poverty is the oft-mentioned observation that, in certain boarding or public schools of England, such as Eton College and Beaumont College, attended by sons of the well-to-do, the incidence of rheumatic fever is very low in the school populations, in spite of the fact that the schools are situated in districts in which the disease is prevalent.

From other countries the importance of poverty and all its attendant conditions as a predisposing factor in rheumatic fever has not been emphasized with so much vigor. However, Nobel,⁸ in Germany, believes that rheumatism is a disease of the poor. In the United States Faulkner and White⁹ obtained data from colleges and private preparatory schools and concluded that rheumatic infections and rheumatic heart disease were less common among this comparatively well-to-do group. Swift¹⁰ states that: "apparently, poverty, malnutrition, and unhygienic surroundings furnish the most favorable human soil for the development of this infection. Many cases are seen, however, among well-to-do members of society."

In the face of these statements, backed by more than suggestive evidence, it would seem important to go further into an analysis of the situation in this country. Does poverty really predispose to rheumatic fever, and, if so, to what extent? The answer is important because such facts concern an evaluation of environmental influences which predispose to this obscure disease, and knowledge of them may be of some value in the field of prevention. For their determination we would like to know the incidence of rheumatic fever among different strata of society in various widely scattered communities. At the moment, however, such data are not available, for, on the one hand, the stratification of a given American population according to different social and economic standards is not as clearly defined as in England; on the other hand, the incidence of rheumatic fever, or the mortality rates justly attributed to this disease, are practically unknown quantities in

this country. To our knowledge, it is a reportable disease only in a few countries or communities, and unfortunately rheumatic lesions are not accurately reflected in mortality statistics.

Perhaps the nearest practical approach which at present can be made to an estimation of the incidence of this disease is the determination of the incidence of rheumatic cardiac lesions in a given population. We recognize fully that the incidence of rheumatic fever and that of rheumatic heart disease may be two quite different things and that the rate of development of the cardiac manifestations of rheumatic fever may be an indication of the type of therapy to which rheumatic patients are subjected, rather than an expression of the actual incidence of rheumatic fever. However, even if it were possible to obtain data on the incidence of *rheumatic fever* in a few selected groups of individuals we would not have any general figures with which to compare them, whereas rough statistics on the incidence of *heart disease* in various populations do exist.

With this thought in mind we have recently reviewed the incidence of rheumatic heart disease in a group of Yale University undergraduate students, as the first of a series of studies which we hope to make on the incidence of rheumatic heart disease in differently selected populations. With the University population we are dealing with a selected group of young male adults, most of whom come from the northeastern part of the United States, and among whom there is a high percentage from so-called upper economic strata. It is our immediate purpose to compare the incidence of rheumatic heart disease in this group with other groups, selected from the literature, and also to analyze roughly the distribution of rheumatic cardiac disease according to the economic status of the men within the group itself. In other words, the questions to be answered from these data are: (a) Is rheumatic heart disease as common among our group of University students as it is supposed to be among individuals of similar age from other walks of life; (b) is there a higher incidence of rheumatic heart disease among students representing poorer families than among those representing families which are better-to-do? The choice of the student group as a favorable population in which to pursue such a study lies mainly in the fact that it contains a fair number of representatives of well-to-do families, a feature not present in groups of industrial employees, recruits, etc., which have been subjected to similar incidence studies. Whatever results are obtained from such a well-to-do group should, however, be eventually evaluated by comparison with incidence figures drawn from the poorer sections of city and rural districts.

Methods. *Selection of Cases.* To obtain our data, the medical histories of 7914 undergraduate students and 4455 male graduate students were reviewed. The records examined, which are compiled

and kept by the Yale University Department of Health, covered all undergraduates enrolled in the classes of 1920 to 1930, inclusive, and all male graduate and professional school students matriculating at the University during the period from 1920 to 1930, who had undergone physical examinations conducted by the University Department of Health during their period of matriculation. Each undergraduate student's record includes from one to four complete, annual, physical examinations, together with form letters from the parents and a completed form by the student, briefly describing the past medical history. In a high percentage of the group are also included records of illness contracted during their period of matriculation.

The number of complete physical examinations per man varied somewhat during this period. Members of the undergraduate classes of 1920 and 1922, inclusive, underwent a single physical examination; those of the classes of 1923 and 1924 underwent two examinations, at the beginning and end of their course, respectively; those of the classes of 1925 to 1930, inclusive, underwent four examinations, one during each of the years in which the individual was enrolled as an undergraduate. It is evident, therefore, that a progressive increase in the thoroughness in which the physical data were obtained exists.

The histories of the entire group were first gone over by an experienced clerk,* and from them all those were selected in which were recorded cardiac lesions, or abnormalities of cardiac function of any kind, exclusive of so-called functional cardiac murmurs. The selected cardiac records were then gone over by one of us, and from them were chosen those cases which could be logically interpreted as examples of rheumatic heart disease. The diagnosis of rheumatic heart disease had not been made in many instances by the examining physician; such terms as mitral regurgitation, chronic endocarditis, etc., were employed instead, but in a surprising number of what might have been questionable cases the student gave a history of rheumatic fever. Clinical judgment was required in order to arrive at a decision in a fair number of cases. In these the following criteria were employed: All cases of mitral stenosis were accepted as examples of rheumatic heart disease, all cases of endocarditis, and of mitral and aortic insufficiency, in which the student gave a history of either rheumatic fever or heart trouble following scarlet fever were also accepted. The remaining number of questionable cases turned out to be relatively small, for in most instances the examining physicians had made every effort to determine whether or not suggestive signs were actual manifestations of organic heart disease, and in nearly all such instances the student had been examined by a heart specialist.

* We are particularly indebted to Miss Mildred A. Mahoney for her assistance to us in this aspect of the work.

Control Disease Groups. It is difficult to find a common clinical condition which is truly comparable to inactive rheumatic heart disease, that is, a common disease which is generally contracted during childhood and in which evidence of old (or active) lesions can be detected on physical examination during young, adult life. Although neither of the two control conditions which we finally selected proved truly satisfactory, they seemed to be the best at our disposal—they included: (1) Clinical tuberculosis, and (2) allergic diseases, such as bronchial asthma and hay fever. In the first, *i. e.*, clinical tuberculosis, we recognize that straitened economic circumstances may play a heavy predisposing rôle which can be reflected in incidence statistics; in the second, *i. e.*, allergic diseases, it has been maintained that the reverse is true, namely, that these conditions find a higher incidence among better-to-do members of society.* The criteria on which these control cases were selected from the group of 7914 undergraduate students were as follows: (1) Tuberculosis. This included students who developed clinical tuberculosis during their college course and those who showed evidence of old tuberculosis detectable by physical examination, or who gave an unequivocal history of having had clinical tuberculosis and having been under treatment. In all of the latter instances, letters from physicians or sanatoria referring to the patient's condition accompanied the student's history. (2) Allergic conditions. This included students who showed active manifestations of these conditions during their college course, and those who gave a history of severe, or moderately severe, asthma or hay fever within 5 years prior to their admission to the University.

Method of Evaluating Financial Status. Three methods of approach were chosen to determine the financial status of the families from which students with rheumatic heart disease or the control diseases came:

(a) The character of the preparatory schools which they had attended. These were arbitrarily divided into four groups: (1) Boarding schools—Grade I, more expensive; (2) boarding schools—Grade II—less expensive; (3) private day schools; (4) high schools.

(b) Whether or not the student had been self-supporting during his period of matriculation, *i. e.*, had applied to the University Bureau of Appointments during his college course.

(c) Whether or not he had held a scholarship in order to defray tuition expenses.

As about 90 per cent of first attacks of rheumatic fever seem to

* This point does not seem to have been emphasized in many of the recent works which we have consulted on asthma and hay fever and, in fact, is denied in one of them;¹¹ but the statement, that bronchial asthma and hay fever is an affection which belongs peculiarly to the upper ranks of society, may be found in many of the older textbook articles, such as those in Allbutt's *System of Medicine*, 1898; Nothnagle's *Encyclopedia of Practical Medicine*, American edition, 1902; and Osler's *Modern Medicine*, 1907.

occur before the age of 15 years,^{12,13} we were more interested in ascertaining the financial status of the student's family during his childhood than the financial status of the student himself while a matriculant. In this respect method (a), *i. e.*, the preparatory school grading, may be a little more adequate than methods (b) and (c). In criticism of all three methods it must be said that they have obvious limitations. The figures obtained can only be judged insofar as they can be compared with similar figures obtained from the total contemporary University population, and, if these methods are at all adequate, the control diseases should give significant, predictable deviations from the mean.

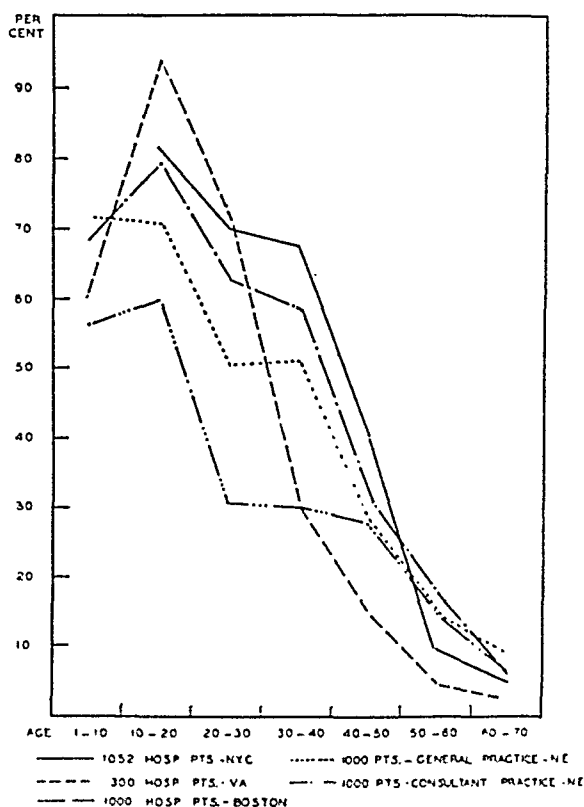


FIG. 1.—The percentile age distribution of rheumatic heart cases in five groups of cardiac patients.

The Incidence of Rheumatic Heart Disease Among Young Male Adults in the United States. There are few observations recording the incidence of rheumatic heart disease in various American populations with which our results can be compared and, so far as we can find, there are none which actually record direct observations on the actual incidence of rheumatic heart disease among large groups of young male adults. One may arrive, however, at an

indirect estimation from statistics based on the incidence of cardiac disease of all types. Roughly it has been accepted that the total incidence of heart disease of *all types* among public school children in eastern North American cities lies somewhere between 6 and 20 per 1000; among young North American adults, *i. e.*, under 30 years, between 15 and 34 per 1000.* These various estimates are dependent upon the manner in which a given population has been selected—its age distribution, its geographic location and the diagnostic criteria employed in determining what constitutes cardiac disease. Unfortunately we cannot accurately evaluate these variants unless they are all specified in each report, which does not happen to be the case. Space does not permit a discussion of the relative importance which each may play, but one of us has assembled data in another publication which deals with this aspect of the problem, to which the reader may be referred.¹⁵ There is, however, one variant, namely, age, which lends itself to analysis more readily than some of the other variants, and which is furthermore an expression of the different etiologic types of heart disease within the group. For instance, we may be sure that in the north-eastern part of the United States most cardiac disease which occurs in individuals under 25 years is due to rheumatic fever, if we draw upon the figures of Wyckoff and Lingg,¹⁶ Wood, Jones and Kimbrough,¹⁷ and White and Jones,¹⁸ whose observations in various selected cardiac populations have been charted in Fig. 1. There are wide differences in some of the determinations listed here, but, by and large, all tend to emphasize the importance of rheumatic fever as a cause of heart disease in the first three decades of life.

TABLE 1.—ESTIMATED INCIDENCE OF RHEUMATIC HEART DISEASE AMONG GROUPS OF YOUNG ADULTS.

Character of population.	Size of population.	Age.	Observed incidence of heart disease per 1000.	Estimated per cent of total heart disease which is rheumatic.	Estimated incidence rheumatic heart disease per 1000.
Troops . . . United States Draft, 1918 ¹⁹	2,510,751	21 to 30	26.26	60	15.7
North—White	10,005	21 to 30	34.15	60	20.4
South—White	10,571	21 to 30	24.60	60	14.7
South—Negro	5,239	21 to 30	29.07	60	17.8
East	7,934	21 to 30	35.56	60	21.3
Insurance . . Metropolitan Life Insurance Company 1921 ²⁰	861	Under 25	17.00	65	11.0
Industry (male) . . . Garment workers ²¹	2,107	80% below 40	23.00	56	12.8
Working boys (N. Y. C.) 1930 ²²	2,691	14 to 17	16.00	77	12.3
Students . . . Harvard University 1915 ²³	662	18	19.4†	72+	13.9+

* Cohn has assembled various incidence figures for heart disease in his excellent review of Heart Disease from the Point of View of the Public Health.¹⁴ Most of our general incidence data have been derived from his paper, supplemented by additional data which one of us has assembled elsewhere.¹⁵

† Valvular disease of the heart.

Included in Fig. 1 is a series of 300 patients from Virginia, in which, although the total incidence of rheumatic heart disease in this group is lower, the age curve conforms to that found in the North.

Armed with these facts we may then approach statistics on the incidence of cardiac disease in large groups comparable as to age and sex with those of our University students. These appear in Table 1. Here are recorded the observed incidence of heart disease in various populations, together with estimates of the expected percentages (taken from data in Fig. 1) of *rheumatic heart disease* in the different age groups. We assume as a conservative estimate that, of the heart disease occurring between the ages of 15 and 20 years, at least 75 per cent is due to rheumatic fever; between the ages of 20 and 25 years, 65 per cent; between the ages of 25 and 30 years, 55 per cent. Such estimates give us incidence figures for rheumatic heart disease in the populations listed in Table 1 (roughly representing the age group of 14 to 30 years). They prove to be between 11 and 21.3 per 1000. The lowest figure is recorded among individuals applying for insurance, and the highest among men from the eastern part of the United States who were examined by the Draft Boards. On this basis as a conservative average for the incidence of rheumatic heart disease among young adult men between the ages of 18 and 25 years, who represent the general population of the northeastern part of the United States, one might take the figure of 15 per 1000, and it is with this figure that our subsequent studies in the University group will be compared.

Results. *Age Distribution of the Student Population of Yale University.* In Fig. 2 is shown the age distribution of undergraduate and graduate students attending Yale University during the years of 1920 to 1930. The graphs record the age on entering the University. One may assume that the average leaving age is approximately $3\frac{1}{2}$ years higher for undergraduates and 3 years for the graduate and professional school students. In the first group, therefore, we are dealing with a population in which most of the students fall between the ages of 17 and 24 years; in the second, between the ages of 19 and 30 years.

Incidence of Rheumatic Heart Disease Among Yale University Students. The observed incidence of rheumatic heart disease, which we obtained by methods outlined above, proved to be 8.2 per 1000 for the undergraduate group and 11.4 per 1000 for the graduate group. (See Table 2.) Both of these figures lie below that which we have assumed to be the average rate for the general population in the northeastern part of the United States, namely, 15 per 1000. The explanation of the higher incidence between the undergraduate and graduate group is not clear. Obviously the latter are older, as shown in Fig. 2, but there are also certain differ-

ences in the general make-up of the two groups. One of these differences is perhaps best expressed by a fact, which will be enlarged upon later, that among the undergraduate students approximately 75 per cent have entered college from private schools as opposed to high schools; whereas, among the graduate and professional students we find that almost 60 per cent of them had entered college from high schools. It is also pertinent to consider this observed higher incidence of rheumatic heart disease in graduate students in the light of similar experiences with tuberculosis, for it is our belief that, in spite of expected differences attributable to age, clinical tuberculosis also finds a much higher incidence

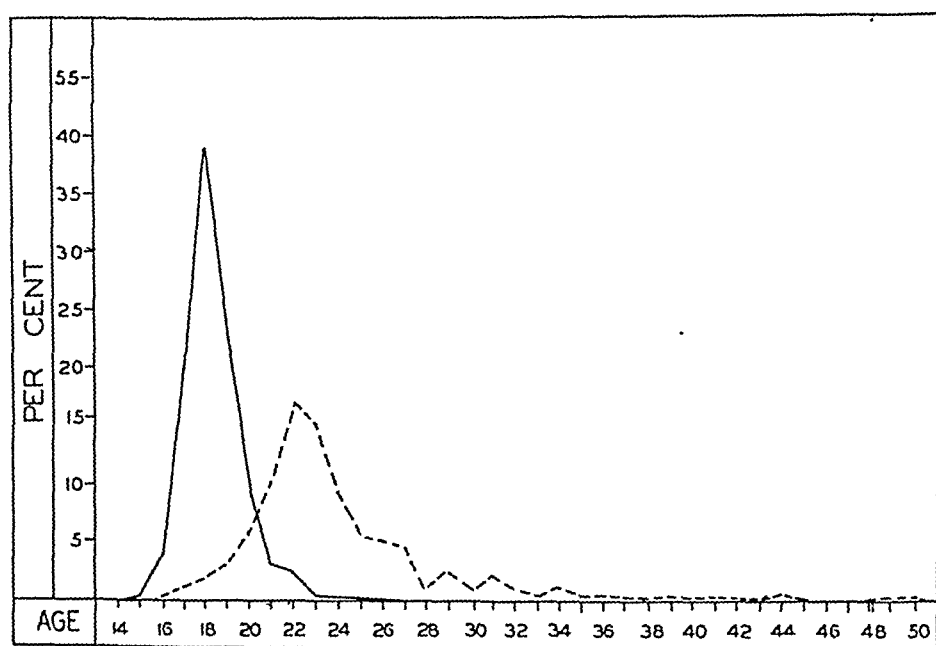


FIG. 2.—The age distribution of Yale University students. The broken line represents the entering age of graduate students; the solid line, of undergraduates.

among the graduate students of Yale University than among the undergraduates.* In the present study of our control groups, for instance, which has been based on criteria mentioned above, the case rate of tuberculosis among graduate students was more than double that for the undergraduates.

From figures in Table 1 it will be seen that in 1915 the incidence of valvular disease of the heart among 695 Harvard freshmen was found by Lee²³ to be 19.4 per 1000, a figure which is far higher than that found among our undergraduate or graduate students. Whether there are certain inherent differences in the two University

* Recent observations by Dr. E. L. Opie and his associates also point to a considerably higher incidence of tuberculosis among medical students than among college students.²⁴

populations or not, we are not prepared to say, any more than we are prepared to claim leadership on the basis of these figures in a health contest between these two institutions in which rivalries of other types have been tested before.

TABLE 2.—RHEUMATIC HEART DISEASE INCIDENCE IN STUDENT POPULATION.

Character of student population.	No. in group.	No. of cases rheumatic heart disease.	Rate per 1000.
Undergraduates—Classes 1920 to 1930	7914	65	8.2
Graduate students, 1920 to 1930	4455	51	11.4
<hr/>			
Undergraduates classified according to:			
A. Preparatory schools:			
Boarding schools—Grade I	1878	11	5.8
Boarding schools—Grade II	1996	11	5.5
Private day schools	1809	12	6.6
High schools	2231	28	12.5
Total	7914	62*	
B. Self-support:			
Nonself-supporting	4995	37	7.4
Self-supporting	2919	26	8.9
Total	7914	63*	
C. Scholarships:			
Without scholarships	6791	53	7.8
With scholarships	1123	10	8.9
Total	7914	63*	

* Of the original total of 65 cases, data with regard to preparatory schools, self-support and tuition were not available in 2 or 3 instances.

Incidence of Rheumatic Heart Disease in the Various Economic Strata of Students.—The analysis of the economic status of students has been confined to the undergraduate group alone.

(a) *Preparatory Schools.* Our first attempt to grade the economic status of the families of students with rheumatic heart disease has been based on the character of the schools at which individual boys had prepared for college. As already stated, this is not an accurate index of affluence or penury, for many sons of rich manufacturers attend high schools, and many sons of poor college professors attend boarding schools in which the tuition fees are quite out of keeping with the professor's salary. Furthermore, an element of selection may enter the problem as boys with rheumatic heart disease may not be sent away to boarding school, or, for that matter, to college with the same frequency as their healthier fellows. Nevertheless, these attempts to grade the families on the preparatory school basis seem to be significant, if only from the fact that in the case of our control diseases, *i. e.*, tuberculosis, bronchial asthma and hay fever, in one of which the effect of economic status has been

particularly recognized, the results fall out as one might have predicted.

Our preparatory school findings appear in diagrammatic form in Fig. 3. Here the average distribution of the type of schools which had been attended by undergraduate students of the classes 1920 to 1930 is shown in the first left-hand column. It will be seen that only 26 per cent of the 7914 men in this group had entered college directly from high schools, while almost 50 per cent had entered from boarding schools. Of the small group of students with rheumatic heart disease, shown in the next column, 45 per cent

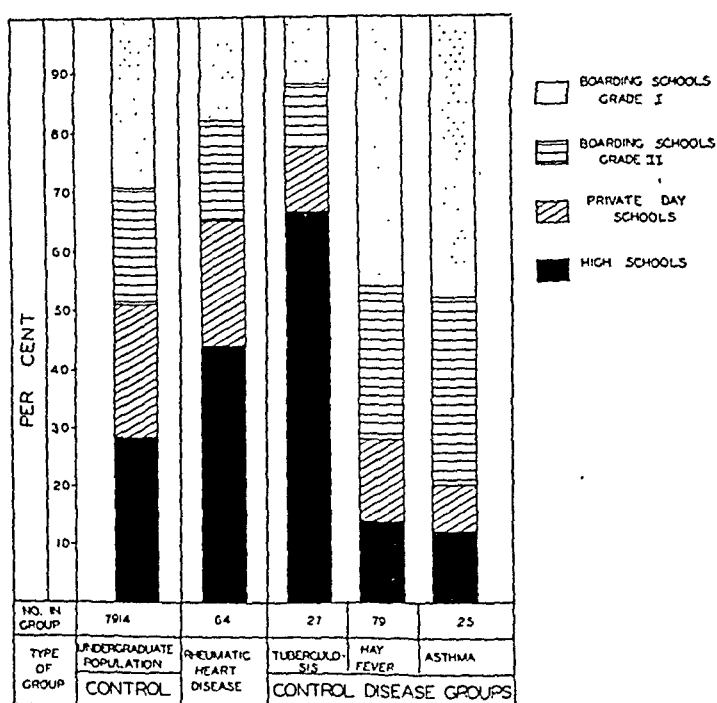


FIG. 3.—The relative percentages of preparatory schools represented by undergraduates of the Classes of 1920 to 1930, as compared with similar percentages from a group of students with rheumatic heart disease, and other control disease groups.

had come from high schools, and of the students with tuberculosis, 65 per cent had come from high schools. In sharp contrast stands the group of men with allergic diseases in which only 12 per cent had come from high schools. This last finding would seem to bear out the contentions which appear in older textbook articles on bronchial asthma and hay fever, to which we have already referred. We recognize, of course, that our method of approach in these latter conditions may not give us a true indication of actual incidence, but rather the incidence of cases of bronchial asthma and hay fever concerning which either a physician was consulted, or the patient was sufficiently aware of his symptoms to list them in his past

medical history. The same may be said, of course, of our tuberculosis controls.

If our results are expressed in a different manner, as shown in Table 2, we find that the incidence of rheumatic heart disease in boys who had attended expensive boarding schools is only 5.8 per 1000, in contrast to 12.5 per 1000 among boys from high schools.

(b) and (c). *Self-supporting and Scholarship Students versus Students Who Are Non-self-supporting and Without Scholarships.* In Fig. 4 are shown the relative percentages of men in the total undergraduate population who were wholly or partially contributing to their own support, and also those who held scholarships to

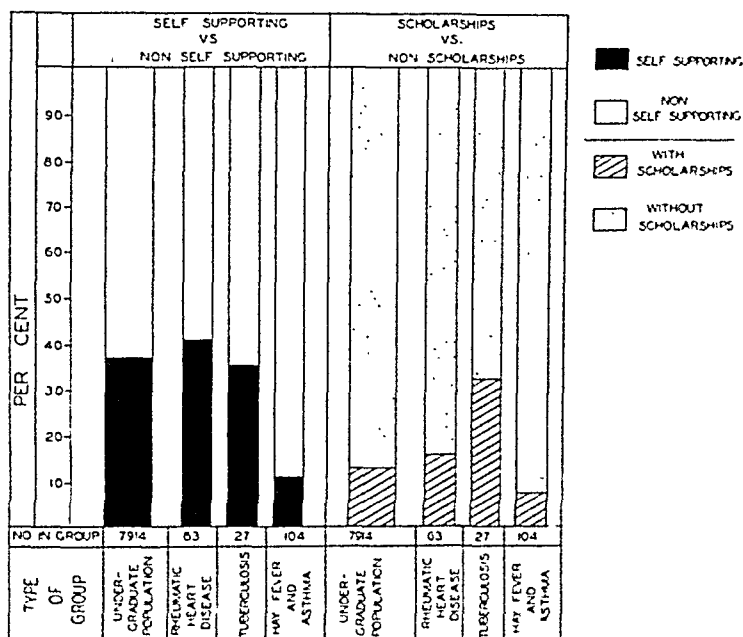


FIG. 4.—The relative percentages of self-supporting students, and students with scholarships in the undergraduate classes of 1920 to 1930, as compared with students with rheumatic heart disease, and other control disease groups.

defray tuition expenses, as compared with these conditions in students with rheumatic heart disease and the other control disease groups. Here again these two methods of evaluating the economic status of students have obvious limitations. In particular, one might well say that the holding of a scholarship is supposedly first and foremost an attribute of mental ability rather than that of limited means. Nevertheless, the control diseases fall out more or less according to the expected ratio, although the demonstration is by no means so marked as in the grading on the basis of preparatory schools. In the case of the rheumatic group it will be seen in both instances, that, if these criteria are a measure of financial

status, the student with rheumatic heart disease is a shade poorer than the average student, but it is questionable whether such minor differences are of any significance. These same data expressed in a different manner also appear in Table 2.

Discussion. By and large, one may conclude from a study of this type that there is some evidence to support the fact that the incidence of rheumatic heart disease is lower among well-to-do individuals than it is among the rank and file, but this feature has proved to be a more difficult thing to prove by the present methods employed than we had anticipated. Within the limitations of our methods one can at least say that the incidence of rheumatic heart disease in a group of almost 4000 men who have prepared for college at boarding schools is well below that of the general population; in fact, it is almost one-third of the expected incidence. Furthermore, the rate or incidence in this group is less than one-half that of the rate in a group of men who prepared for college at high schools. Apart from this, however, the figures are not very significant. It is true that the total incidence of 8.2 per 1000 for the whole undergraduate group is well below the expected average of 15 per 1000, but the difference is not particularly striking. Certainly the statement from England, which we have already quoted, that there is no disease which has a clearer cut "social incidence" than acute rheumatism, is not strikingly reflected in our figures, but we do not as yet have data from poverty-stricken districts with which we may test this thesis.

Conclusions. 1. The incidence of rheumatic heart disease in a group of 7914 undergraduate students of Yale University has been found to be 8.2 per 1000, as compared with 15 per 1000 which is an average figure obtained from statistics of comparable age groups of individuals in other walks of life.

2. Among the men in this group who had attended expensive boarding schools the incidence was only 5.8 per 1000 as compared with 12.5 per 1000 among those from high schools.

3. The contention that rheumatic fever is a disease which finds a lower incidence among people of ample means finds support in these observations.

4. According to the methods employed the factor of poverty does not, however, seem to be as important a predisposing rôle in determining the incidence of rheumatic heart disease as it does in clinical tuberculosis.

BIBLIOGRAPHY.

1. Miller, R.: Report on the Environmental and Other Predisposing Causes of Rheumatic Infection, Suppl., Brit. Med. J., July 3, 1926.
2. Glover, J. A.: Milroy Lectures on the Incidence of Rheumatic Diseases: I. Incidence of Acute Rheumatism, *Lancet*, 1930, 1, 499.
3. Child Life Investigations: Social Conditions and Acute Rheumatism, Special Report Series of the Medical Research Council, No. 114, London, His Majesty's Stationery Office, 1927.
4. Hutchison, R.: The Value of Pulse Charts in Acute Carditis in Childhood, *Lancet*, 1922, 1, 1086.

5. Coombs, C. F.: Rheumatic Infection of Childhood, *Lancet*, 1927, 1, 579, 634.
6. Campbell, M., and Warner, E. C.: A Study of Rheumatic Disease in Children, *Lancet*, 1930, 1, 61.
7. Thomson, A. P.: Discussion on Rheumatic Infection in Childhood, *Brit. Med. J.*, 1925, 2, 794.
8. Nobel, E.: Statistik und Prophylaxe der Klappenfehler, *Wien. klin. Wchnschr.*, 1928, 41, 125.
9. Faulkner, J. M., and White, P. D.: The Incidence of Rheumatic Fever, Chorea and Rheumatic Heart Disease With Especial Reference to Its Occurrence in Families, *J. Am. Med. Assn.*, 1924, 83, 425.
10. Swift, H. F.: Rheumatic Fever, *Cecil's Textbook of Medicine*, Philadelphia, W. B. Saunders Company, 1927.
11. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C Thomas, 1931, p. 178.
12. Wilson, M. G., Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in the Classification of Heart Disease: III. Heart Disease in Children, *Am. Heart J.*, 1928-1929, 4, 164.
13. Paul, J. R.: Age Susceptibility to Familial Infection in Rheumatic Fever, *J. Clin. Invest.*, 1931, 10, 53.
14. Cohn, A. E.: Heart Disease From the Point of View of the Public Health, *Am. Heart J.*, 1927, 2, 275, 386.
15. Paul, J. R.: The Epidemiology of Rheumatic Fever: A Preliminary Report With Special Reference to Environmental Factors in Rheumatic Heart Disease and Recommendations for Future Investigations, New York, Metropolitan Life Insurance Company Press, 1930.
16. Wyckoff, J., and Lingg, C.: Statistical Studies Bearing on Problems in the Classification of Heart Disease: II. Etiology of Heart Disease, *Am. Heart J.*, 1926, 1, 446.
17. Wood, J. E., Jones, T. D., and Kimbrough, R. D.: The Etiology of Heart Disease, *Am. J. Med. Sci.*, 1926, 172, 185.
18. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *Am. Heart J.*, 1928, 3, 302.
19. Love, A. G., and Davenport, C. B.: Defects Found in Drafted Men, Washington, D. C., Government Printing Office, 1920.
20. Dublin, L. I., Fisk, E. L., and Kopf, E. W.: Physical Defects as Revealed by Periodic Health Examinations, *Am. J. Med. Sci.*, 1925, 170, 576.
21. Schereschewsky, J. W., and Tuck, D. H.: Studies in Vocational Diseases: I. The Health of Garment Workers, *Public Health Bull.*, No. 71, Washington, D. C., 1915.
22. Metropolitan Life Insurance Company, *Statistical Bull.*, 1930, 11, No. 2.
23. Lee, R. I.: Preventable Heart Disease, *Boston Med. and Surg. J.*, 1915, 173, 157.
24. Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: Tuberculosis in Medical Students, *Trans. Assn. Am. Phys.*, 1931, 46, 237.

THE IMMEDIATE CAUSES OF DEATH IN CANCER.

BY SHIELDS WARREN, M.D.,

PATHOLOGIST, NEW ENGLAND DEACONESS AND COLLIS P. HUNTINGTON MEMORIAL
HOSPITALS; INSTRUCTOR IN PATHOLOGY, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

(From the Laboratory of Pathology, New England Deaconess Hospital, and the
Department of Pathology, Harvard Medical School.)

BUT little information exists as to the actual immediate causes of death in cases of cancer. This is largely because in mortality statistics cancer appears alone as the cause of death in cases of that disease. In the course of a study of the cases of cancer which

came to autopsy in the laboratories of the New England Deaconess Hospital, the Collis P. Huntington Memorial Hospital, the House of the Good Samaritan and the Pondville State Hospital, the immediate cause of death in each case was determined as accurately as possible from a study of both the clinical record and the postmortem protocol of the patient.

In the present paper the findings in 500 cases of carcinoma are presented. These cases were selected at random, but sarcoma, lymphoblastoma, leukemia, etc., have been excluded. There are practically no cases of cancer in children included.

By the use of material from four hospitals the variation in picture due to the tendency of certain hospitals to have more of given types of cases than others has been largely compensated for. Moreover, among these hospitals there are not only beds for early or "active" cases of cancer but for terminal-care cases as well, so that the proportion of deaths due to accidents of treatment is not as large as it appears to be in statistics from a general hospital. A certain number of deaths of this latter type is inevitable in view of the very extensive condition of the disease in many cases at the time they present themselves for treatment.

The distribution of cases in this study is compared in Table 1 with that in the Massachusetts mortality statistics for 1930. It will be noted that the number of cases primary in the buccal cavity, skin, female genitalia and breast are definitely higher in the study group, and cancer primary in the stomach and liver and unspecified organs much lower. This distribution is to be expected, as the groups of stomach and liver and of unspecified organs are naturally abnormally large in mortality returns based largely on clinical observations. This discrepancy is particularly noted in the group of cancers of the stomach and liver, which comprises over one-fourth of the general group and only one-ninth of the study group.

TABLE 1.—DISTRIBUTION OF FATAL CASES OF CANCER BY PRIMARY SITE.

	Total cases.	Buccal cavity, per cent.	Stomach and liver, per cent.	Peritoneum, intestine and rectum, per cent.	Female genitalia, per cent.	Breast, per cent.	Skin, per cent.	Other or unspecified organs, per cent.
Mass. statistics, 1930	5813	3.2	28.4	19.2	13.4	11.1	1.6	23.2
Study group	500	11.0	11.0	18.0	20.0	17.4	4.6	18.0

Cancer of the buccal cavity and of the skin is somewhat heavily weighted in the study group, because of the numbers of these cases treated in the outpatient department of the Huntington Hospital, some of which fail to respond to treatment and are later admitted to the house.

The distribution of cases in the study series is not too far at

variance with that given for the population of Massachusetts and apparently represents a fair sample of the fatal cases of cancer.

The most commonly occurring of the various causes of death is cachexia. This term was utilized only in those instances where the clinical course of the disease was characterized by progressive wasting and weakness, accompanied by increasing anemia. Cachexia has not been considered the immediate cause of death if any lesion sufficient in itself to be fatal has been discovered. It may, therefore, be regarded as considerably more frequent than is recorded here. It is striking that in almost all instances of death due to cachexia, of which there were 114 in the present series (more than 22 per cent), there had been considerable necrosis of the tumor tissue, due either to ulceration and secondary infection or to interference with the blood supply of the tumor.

In a number of cases where death was due to definite anatomic causes cachexia was present to a greater or less degree, but in most of these the cachexia could be definitely established as secondary to sepsis, hemorrhage or other lesion which was considered as the immediate cause of death.

Startling to the novice is the large number of fatal cancer cases in which excellent nutrition and not infrequently obesity are maintained to the end.

In carcinoma of the breast and carcinoma of the stomach one finds the largest proportion of deaths from cachexia (33.3 and 45.2 per cent, respectively), and in carcinoma of the bladder the least (4.3 per cent). (Table 2.) When the cases of cachexia are studied in relation to organs involved (Table 3) the rectum-colon group becomes even more important than the stomach. The carcinomas of the breast, as may be seen from Table 3, caused over one-fourth of all the deaths from cachexia. The next most frequent lesions were carcinoma of the rectum and colon with 17.5 per cent, and of the stomach with 16.7 per cent. The bladder and the prostate each were the primary sites in less than 1 per cent of the cases dying from cachexia.

The relatively high incidence of pneumonia (14 per cent), particularly bronchopneumonia, would be expected in a group such as this where the age level is relatively high and resistance to infection is naturally considerably lowered. Bronchopneumonia is much more common than lobar. There were 64 cases of bronchopneumonia and only 6 cases of lobar pneumonia. These cases of lobar pneumonia may be regarded as intercurrent infections, having very little immediate relation to the underlying disease process. With their almost inevitable interference with the respiratory passages and the excellent opportunity for inhalation and aspiration of foreign material, the carcinomas of the lip and pharynx provided 24.3 per cent of the cases of pneumonia. Moreover, in this same group of cases pneumonia is by far the most common single cause of death, amounting to 36.2 per cent. (Table 2.)

TABLE 2.—THE FREQUENCY OF COMMON CAUSES OF DEATH IN CARCINOMA OF SPECIFIED ORGANS.

	Total number.	Cachexia.		Pneumonia.		Renal insufficiency.		Peritonitis.		Pulmonary insufficiency.		Embolus (pulmonary).		Other causes.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Bladder	23	1	4.4	2	8.7	17	73.9	1	4.4	—	—	1	4.4	1	4.4
Breast	87	29	33.3	10	11.5	2	2.3	3	3.5	19	21.8	3	3.5	21	24.1
Cervix uteri	64	10	15.6	16	9.4	27	42.2	9	14.1	1	1.6	3	4.7	8	12.5
Colon and rectum	90	20	22.2	13	14.4	1	1.1	21	23.3	—	—	5	5.6	30	33.3
Pharynx (also lip and tongue)	47	7	14.9	17	36.2	—	—	—	—	—	—	1	2.1	22	46.8
Prostate	19	1	5.3	2	10.5	12	63.2	—	—	—	—	2	10.5	2	10.5
Skin, face	20	5	25.0	7	35.0	1	5.0	1	5.0	—	—	—	—	6	30.0
Stomach	42	19	45.2	4	9.5	1	2.4	10	23.8	—	—	—	—	8	19.1

TABLE 3.—DISTRIBUTION BY LOCATION OF CARCINOMAS IN CASES OF DEATH FROM ASCERTAINED IMMEDIATE CAUSES.

	Total number.	Bladder.		Prostate.		Breast.		Uterus (cervix).		Uterus (fundus).		Skin (face).		Pharynx, lip, tongue.		Esophagus.		Stomach.		Rectum and colon.		Other organs.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Cachexia	114	1	0.9	1	0.9	29	25.4	10	8.8	2	1.8	5	4.4	7	6.1	3	2.6	19	16.7	20	17.5	17	14.9
Pneumonia	70	2	2.9	2	2.9	10	14.3	6	8.6	—	—	7	10.0	17	24.3	4	5.7	4	5.7	13	18.6	5	7.1
Pulmonary insufficiency	25	—	—	—	—	19	76.0	1	4.0	—	—	—	—	—	—	—	—	—	—	—	—	5	20.0
Pulmonary embolus	24	1	4.2	2	8.3	3	12.5	3	12.5	2	8.3	—	—	1	4.2	1	4.2	—	—	5	20.8	6	25.0
Peritonitis	56	1	1.8	—	—	3	5.4	9	16.1	5	8.9	1	1.8	—	—	1	1.8	10	17.9	21	37.5	5	8.9
Renal insufficiency	65	17	26.2	12	18.5	2	3.1	27	41.5	2	3.1	1	1.5	—	—	—	—	1	1.5	1	1.5	2	3.1
Hemorrhage	20	—	—	—	—	—	—	1	5.0	2	10.0	2	10.0	6	30.0	—	—	1	5.0	—	—	8	40.0
Hepatic insufficiency	20	—	—	—	—	6	30.0	1	5.0	—	—	—	—	—	—	—	—	1	5.0	5	25.0	7	35.0
Intestinal obstruction	20	—	—	—	—	2	10.0	2	10.0	1	5.0	—	—	—	—	—	—	—	—	12	60.0	3	15.0
Other causes	86	1	1.2	2	2.3	13	15.1	4	4.7	1	1.2	4	4.7	16	18.6	8	9.3	6	7.0	13	15.1	18	20.9

In the deaths from renal insufficiency (13 per cent of the total) are included those cases which died with definite signs or symptoms of uremia, and where at autopsy there was found hydronephrosis, pyonephrosis, pyelonephritis or multiple abscesses of the kidneys. The very few cases of true nephritis encountered in this series are included under the heading "Cardiorenal." By far the greatest number of deaths from renal insufficiency are caused by carcinoma of the cervix uteri, 41.5 per cent. Carcinoma of the bladder accounted for 26.2 per cent and carcinoma of the prostate 18.5 per cent.

Ureteral obstruction in cases of carcinoma of the cervix is usually low, due either to infiltration of the tumor process into the tissues of the posterior bladder wall and about the lower ends of the ureters, or else to compression of the ureters by iliac lymph nodes enlarged through the metastasis of tumor to them. Occasionally post-radiation fibrosis results in obstruction. In the cases of carcinoma of the bladder the obstruction again is usually due to infiltration of the bladder wall, obstructing the ureteral orifices. On the other hand, carcinoma of the prostate produces obstruction at the urethral orifice just as benign hypertrophy of the gland. In contrast to the large number of cases of carcinoma of the cervix producing urinary obstruction, this was present in less than one-seventh of the cases of carcinoma of the fundus uteri.

Peritonitis, occurring most frequently as a postoperative complication or as the result of postradiation necrosis and perforation, but occasionally as the result of direct extension of the tumor, accounted for 56 or 11.2 per cent of the fatalities.

Under the heading "Pulmonary Insufficiency" are included those cases where the immediate cause of death was sufficient destruction of the lung parenchyma by the tumor to produce asphyxia, compression of the lung by pleural exudate secondary to tumor metastases, or massive collapse of the lung. This group of causes contributed 5 per cent of the fatal cases. A closely related cause falling just short of 5 per cent of the total deaths is embolism of the pulmonary artery or embolism to the right heart. Seventy-six per cent of the cases of pulmonary insufficiency are due to the metastases from carcinoma of the breast.

If we lump together the various fatal lesions affecting the lung, that is, pneumonia, pulmonary insufficiency, abscess of the lung and pulmonary embolism, the group assumes even greater numerical importance than cachexia.

Hemorrhage accounts for an extraordinarily small number of the deaths from carcinoma, only 4 per cent in this series. In one-fourth of the cases of hemorrhage the carcinoma is the indirect cause only, since the presence of the tumor had produced a high degree of obstructive jaundice, the underlying cause of the fatal hemorrhage.

In 14 cases it was impossible to establish the immediate cause of death.

TABLE 4.—THE CAUSES OF DEATH BY ORGANS IN 500 CASES OF CARCINOMA.

	Abscess, lung.	Cachexia.	Embolism, heart and lung.	Endocarditis.	Hemorrhage.	Hemorrhage (cerebral).	Hepatic insufficiency.	Intestinal obstruction.	Intracranial pressure.	Cardiorenal.	Peritonitis.	Pneumonia.	Postoperative collapse.	Pulmonary insufficiency.	Renal insufficiency.	Sepsis.	Starvation.	Thrombosis.	Tracheal obstruction.	Not stated.	Total.
Adrenal . . .	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Bladder . . .	—	1	1	—	—	—	—	—	—	—	1	2	1	—	17	—	—	—	—	—	23
Breast . . .	—	29	3	—	—	2	6	2	2	1	3	10	2	19	2	2	—	—	1	3	87
Cecum and colon . .	—	5	1	—	—	—	3	5	—	—	8	4	—	—	2	1	—	—	—	—	27
Cervix . . .	—	10	3	—	1	—	1	2	—	—	9	6	—	1	27	4	—	—	—	—	64
Esophagus . . .	5	3	1	—	—	—	—	—	—	—	1	4	2	—	—	—	—	—	—	—	17
Kidney . . .	—	3	1	—	—	—	—	—	—	—	—	—	—	1	1	1	—	—	—	2	9
Larynx . . .	2	2	—	—	—	—	—	—	—	—	—	3	—	—	—	—	—	1	—	1	9
Lip . . .	1	—	—	—	1	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	5
Liver and ducts . .	—	2	—	2	3	—	4	—	—	—	1	—	—	1	—	—	—	—	—	—	13
Ovary . . .	—	4	—	—	—	—	1	3	—	—	3	—	—	1	1	—	—	—	—	—	13
Pancreas . . .	—	2	2	—	2	—	1	—	—	1	—	2	—	1	—	—	—	—	—	3	14
Pharynx and antrum .	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Prostate . . .	4	5	1	—	2	—	—	—	—	—	—	8	—	—	—	3	—	1	—	1	25
Rectum and sigmoid .	—	1	2	—	—	—	—	—	—	1	—	2	—	—	12	—	—	1	—	—	19
Salivary gland . .	—	15	4	—	—	—	2	7	—	—	13	9	3	—	1	7	—	2	—	—	63
Skin (face) . . .	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
Skin (body) . . .	—	5	—	—	2	—	—	—	1	—	1	7	—	—	1	2	—	—	—	1	20
Stomach . . .	—	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3
Testis . . .	—	19	—	—	1	—	1	—	—	—	10	4	3	—	1	1	—	1	—	1	42
Tongue . . .	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	4
Uterus . . .	4	1	—	—	3	—	—	—	—	—	—	7	—	—	—	—	1	—	—	1	17
Vulva (vagina) . .	—	2	2	—	2	—	—	1	—	—	5	—	—	—	2	1	—	—	—	—	15
Total . . .	16	114	24	2	20	3	20	20	3	3	56	70	11	25	65	24	2	7	1	14	500

Although one would expect the resistance of these debilitated patients to be greatly lowered and although extensive secondary infection is often present in the tumors, sepsis *per se* is an extraordinarily infrequent cause of death, amounting to less than 5 per cent.

One rather striking group of cases, though small, is that which we may call hepatic insufficiency. This group is characterized by jaundice of obstructive type, usually painless, and anorexia, nausea. At autopsy the liver may be much enlarged (4000 to 6000 gm.) but hardly more than 200 to 300 gm. of liver substance remain between the metastatic nodules.

Summary and Conclusions. 1. The immediate cause of death has been studied in 500 cases of carcinoma.

2. Cachexia is the most frequent single cause, although exceeded by the total of the various pulmonary disorders.

3. Cachexia is associated most frequently with cancer of the breast, stomach and large bowel.

4. By far the commonest cause of death in carcinoma of the cervix uteri is renal insufficiency.

5. Sepsis is an unimportant factor in fatal cases.

6. The striking association of carcinoma of the buccal mucosa with pneumonia (36.2 per cent) and with lung abscess (56.3 per cent) emphasizes the rôle of aspiration in the production of these lesions.

OXYGEN THERAPY—A CRITICAL RÉSUMÉ.

By W. H. POTTS, JR., A.B., M.D.,

INSTRUCTOR IN CLINICAL MEDICINE, BAYLOR UNIVERSITY COLLEGE OF MEDICINE,
DALLAS, TEXAS.

(From the Medical Department of the Dallas Medical and Surgical Clinic.)

ANY therapeutic advance must go through a probation period either under controlled conditions in the laboratory or in the longer, harder school of everyday trial. Oxygen therapy has been going through this period. It is the purpose of this paper to attempt to give a résumé of the status of oxygen therapy after a rather intense 10-year probation period.

The Purpose of Oxygen Therapy. The primary purpose of oxygen therapy is the combating of anoxemia, the clinical importance of which has been recognized since Haldane's monumental book, "Respiration" (1922).¹ Knowledge of various aspects of general metabolism has advanced with astonishing rapidity. Rarely, however, is the oxygen content of the blood of routine concern in the minds of most. The reasons for this apparent neglect are, first, that our knowledge of anoxemia is relatively newly acquired and certainly complex; second, that the method of determining the oxygen saturation of the blood needs simplification. Facilities for the determination of the degree of anoxemia are not to be found in the ordinary clinical laboratory, but the time will come, I venture, when the degree of anoxemia in certain diseases will be considered as regularly as the leukocyte count now is in acute appendicitis.

Difficulties in Applying the Statistical Method to an Evaluation of Oxygen Therapy. One of the most frequent arguments used against oxygen therapy is the absence of statistics showing a decrease in the death rate of treated patients, as compared with untreated patients. Mature consideration, however, demonstrates the difficulties in acquiring such statistics. For instance, up to the present time only the severest cases have been selected for treatment. Furthermore, there are too many complex factors which influence the mortality in pneumonia, such as the type of organism, the age of the patient and the presence of bacilleemia, to make it feasible by the statistical method to assign accurately the relative importance of oxygen in this complex group of factors. Oxygen therapy should not be looked upon as a specific measure in pneumonia, for example, any more than we look upon the use of glucose as a specific measure. That glucose is frequently of assistance in the treatment of pneumonia no one questions. Oxygen should be similarly regarded and should receive greater emphasis, if anything, as there is no mechanism in the body for the storage of oxygen.

Terminology. An appreciation of the following definitions is essential to an understanding of the literature on the subject. By procuring samples of arterial² and of venous^{3,4} blood, procedures attended by little if any risk, it is possible by the usual gasometric technique⁵ to determine the oxygen content. A portion of the blood is then saturated with oxygen and the total oxygen capacity is determined. Thus are obtained (1) arterial oxygen content (cubic centimeters of oxygen combined with hemoglobin per 100 cc. of arterial blood); (2) venous oxygen content (a similar value for venous blood); (3) total oxygen capacity (cubic centimeters of oxygen combined with the hemoglobin of 100 cc. of blood when fully saturated).

The difference between the oxygen content and total oxygen capacity has been named by Lundsgaard³ the oxygen unsaturation. This term can be used in speaking of either arterial or venous blood. The unsaturation may be expressed either as cubic centimeters of oxygen per 100 cc. of blood or as percentage of the total oxygen capacity. In the latter the data represent the per cent of total hemoglobin in the form of reduced hemoglobin. The oxygen consumption is the difference between the arterial and venous oxygen content.

Only approximate figures can be given for these factors. An example will make this clear:

	Cubic centimeters.	Per cent.
Arterial oxygen content	18	90 (av. 95)
Venous oxygen content	14	70
Total oxygen capacity	20	100
Arterial oxygen unsaturation	2	10
Venous oxygen unsaturation	6	30
Oxygen consumption	4 (2.6 to 8.3)	20

It is apparent that these terms fail to take into consideration the oxygen tension in the tissues, a factor of the utmost importance. No feasible method is as yet available to render such information accessible. In this very important particular is our knowledge of anoxemia seriously lacking, for surely the justification for the existence of the elaborate mechanisms for absorption and transportation of oxygen is its utilization in the tissues. We must be content at present with a study of the per cent saturation of the arterial and venous blood.

From the studies of Binger,⁶ Stadie,⁷ Harrop,⁸ Pilcher and Harrison,⁹ and others, our knowledge concerning the degree of anoxemia occurring in many conditions is rapidly growing. Some of these will be referred to later.

Cyanosis is the Clinical Test for Anoxemia. While it must be conceded that anoxemia and cyanosis, strictly speaking, are not synonymous terms, still for practical purposes we are obliged at present to rely on the degree of cyanosis as an index of anoxemia

and, indeed, for our indications for oxygen therapy. The relationship between these two conditions is well presented by Peters and Van Slyke.¹⁰ They state, "In conditions such as pneumonia, where both cyanosis and tissue anoxia are caused primarily by incomplete oxygenation of the arterial blood, while hemoglobin content is normal and the onset is too rapid for much tissue adaptation to oxygen deficit, there may be a close parallelism between cyanosis and anoxemic symptoms."

Stadie⁴ has given careful consideration to this subject and finds a definite relationship in pneumonia between the degree of cyanosis and the per cent of arterial unsaturation. With increasing cyanosis the arterial unsaturation becomes greater. The venous unsaturation varies similarly. The following table shows this relationship:

ARTERIAL AND VENOUS OXYGEN UNSATURATION ASSOCIATED WITH CYANOSIS OF VARYING DEGREE.

Cyanosis.	No. of observations.	Unsaturation, per cent.	
		Mean arterial.	Mean venous.
None	18	5.8	23.8
Slight	11	11.8	30.4
Moderate	10	17.2	41.8
Marked	13	26.0	51.2
Intense	4	53.2	82.3

The distribution of the cyanosis is of interest in that the most constant and frequent site was found to be in the end of the finger, especially under the nail. As it became more intense it could next be observed over the entire end of the finger, being more marked on the dorsal aspect. Next to the finger the face showed cyanosis most commonly. Marked hourly variation in this location was common, however, thus making the nail the most constant guide. The importance of avoiding the development of cyanosis, if possible, cannot be overemphasized. Certain irreparable toxic changes are known to occur in vital neural cells in the presence of anoxemia, as has been shown by Cannon^{11,12} and his coworkers, and these may be prevented by the early use of oxygen.

General Symptoms of Anoxemia. When anoxemia is of very rapid onset, loss of consciousness may occur without any warning, as when a miner puts his head into a cavity full of methane gas and drops as though felled by a blow. When he recovers, on breathing pure fresh air for a minute, he really feels that he has been knocked down and acts accordingly, assaulting any one in the vicinity. If anoxemia develops more gradually, the intellect and the senses become dulled without the person being subjectively aware of what has happened. When the anoxemia is relieved the sudden increase in power or in visual acuity comes as a great surprise.

Symptoms similar to those resulting from an overdose of alcohol may be present, such as headache, depression, apathy and drowsiness; or excitement and general loss of self-control. The subject

will sing or shout or burst into tears for no apparent reason. He may be extremely quarrelsome or insolent. Indeed, Palthé¹³ has shown that the symptoms of acute alcoholism, both in animals and men, may be completely suppressed by the breathing of pure oxygen, only to return again, however, as soon as the oxygen is removed.

Understanding is impaired more than sensation. Pain is dulled. Finally, each sense is lost, hearing being retained longest. (This fact suggests the exercise of more circumspection in our remarks at the bedside of a presumably delirious patient.) The subject misjudges the position of things and cannot walk straight. There is great muscular weakness and easy fatigability. We are accustomed to attribute the astonishing delirium so frequently seen in pneumonia largely to the fever and toxemia. As a possible anoxemic symptom this delirium appears in a new guise. Much of the behavior of a delirious pneumonia patient finds an exact counterpart in anoxemia experimentally produced in man and dogs (Greene and Gilbert¹⁴).

Another and often still more serious danger arises from the gradual and insensible failure of judgment. A man suffering from anoxemia will usually insist on going on with what he set out to do. An aviator continues to ascend oblivious of danger; a miner engaged in rescue or exploration work, or in dealing with an underground fire, insists on going on when he is suffering from the anoxemia of CO poisoning and often fights any one who tries to make him desist. Recent ventures into the stratosphere, together with the exuberant growth of aviation, are affording opportunities for very practical utilization of this fund of knowledge.

Delayed Symptoms of Anoxemia. Besides the immediate symptoms there are a number of delayed symptoms or after-effects. These depend partly on the length and partly on the severity of the exposure. One of Haldane's acquaintances has twice knocked down persons on waking up from a short loss of consciousness caused by anoxemia. The best known delayed effect of slight anoxemia is the so-called mountain sickness. A stay of several hours is required to cause this sickness, which usually is felt 8 to 12 hours after the beginning of the exposure. Similarly, a percentage of carbon monoxid, which produces no immediate noticeable effect will, with sufficiently long exposure, cause headache and nausea. At present we can only conjecture as to the nature of the slight temporary pathologic changes of which mountain sickness symptoms are the manifestations.

Adaptation or Acclimatization in Anoxemia. Adaptation or acclimatization may act in two different ways. As Haldane¹ says, "Adaptation may bring it about that the anoxemia which would, without adaptation, exist, is greatly diminished. This form of adaptation is very clearly seen in persons living at great altitudes. In the second place, the tissues may adapt themselves to a lower partial pressure of oxygen. About this second form of adaptation

our knowledge is at present very imperfect; but it seems that clinical evidence points strongly to its existence. Perhaps the clearest evidence is afforded by cases of congenital heart defect. The remarkable point is that in spite of the anoxemic condition of the blood, these people may get on quite well and be able to walk at a good pace. On account of the large increase in the quantity of hemoglobin they have plenty of oxygen in their blood, but at a low partial pressure. It hardly seems possible to doubt, therefore, that their tissues have become adapted to the low partial pressure of oxygen." The fact that anoxemia may exist without harm in chronic cases of disease has certainly contributed to the general failure to recognize the gravity of anoxemia in persons not adapted. Greater knowledge concerning this form of adaptation may conceivably revolutionize our existing ideas regarding anoxemia.

Physiology of Oxygen Therapy. Under normal conditions an individual in bed requires for the maintenance of his metabolism from 15 to 18 cc. of oxygen per breath. Only 21 per cent of the inspired air is oxygen, and since the ordinary tidal air is about 500 cc., this means only about one-fifth of the available oxygen is used. On first thought this appears to be a generous reserve, and indeed is, which Nature has provided for this vital function. In diseased states, however, especially in the presence of fever, the oxygen requirement of the tissues mounts rapidly. Add to this the crippling effect of a marked reduction in the vital capacity of the lungs, as, for example, by a large area of consolidation with its associated edema and inflammatory reaction. An increased pulse rate can partially compensate by hastening the red cells around at a more rapid rate. An increase in the oxygen capacity of the blood also helps.⁷ Gradually oxygen unsaturation increases. The available oxygen in the inspired air remains constant. The respiratory rate increases with its accompanying fatigue, but the amount of air taken in per breath is limited by the vital capacity. The more rapid the respirations the shallower they must be. Hence, the most logical method of breaking this vicious circle would be by increasing the oxygen concentration in the inspired air and, thus, the available oxygen per unit of air.

Mechanisms of Anoxemia in Pneumonia. Consideration of the actual mode of production of anoxemia in pneumonia has brought to light a number of factors, each one of which very probably plays a part. It is apparent that the trouble may be found in either the pulmonary ventilation, the alveolus, the circulating blood or the tissues. Inadequate oxygenation, accordingly, may be due to the following:

1. Failure of adequate ventilation, due simply to rapid, shallow breathing.

2. Some intrinsic alveolar disturbance, due to such factors as:
(a) the mechanical interference by intraalveolar exudate of such

quantity as to prevent access of air, which with intact circulation allows unaërated blood to return to the systemic circulation; (b) dysfunction of alveolar membranes due to edema and faulty nutrition; (c) interference with circulation in alveolar walls, brought about by formation of fibrin plugs within the capillaries. If this interference were extensive enough, either with or without normal alveolar capacity, this would tend to hasten the blood flow through the remaining vascular channels, thereby shortening the duration of contact between blood and air.

3. The intrinsic changes in the circulating blood due to changes in the behavior of hemoglobin with the formation, for example, of methemoglobin.

4. Intrinsic tissue disturbance.

1. FAILURE OF ADEQUATE VENTILATION DUE SIMPLY TO RAPID, SHALLOW BREATHING. Meakins,¹⁵ in 1920, stated that, "Anoxemia occurring in acute lobar pneumonia is a result of the rapid, shallow breathing typical of this condition, which breathing at times scarcely gets air past the dead space in the trachea." Stadie,⁷ however, after careful consideration of this question, concluded on the basis of quantitative considerations that appear irrefutable that the degree of tachypnea observed in any of his cases was incapable of itself of producing anoxemia of the extent encountered. Binger and Davis,¹⁶ out of 16 anoxic pneumonia patients, observed only one in whom the respiration was so shallow (127 cc. tidal air) that a major rôle in producing the anoxia could be assigned to the type of respiration.

2. INTRINSIC ALVEOLAR DISTURBANCE. (a) *Mechanical Interference by Intraalveolar Exudate*. Stadie⁷ first pointed out that "as a rule, when the pneumonia process is confined to one area, as in the typical lobar pneumonia variety, there is little or no cyanosis. The physical signs, viz., dullness, bronchial breathing and a few fine râles, are then confined to the area involved. Kline and Winternitz,¹⁷ and later Gross,¹⁸ have shown that in this type of consolidation there is little or no circulation of blood to the consolidated lung, and therefore little or no admixture of nonaërated with aërated blood occurs. When, however, there is a spread of the pneumonic process and there occur scattered and secondary areas of bronchopneumonia, the blood circulation in these areas is intact. Moreover, there is a more or less widespread bronchitis with peribronchial pneumonia and edema. The lung signs are changed . . . and anoxemia results." Many of the alveoli are functionless due either to occlusion of the bronchioles or to interference by intraalveolar exudate, with the result that unaërated blood is allowed to return to the circulation, thereby augmenting the anoxemia.

(b) *The Dysfunction of Alveolar Membranes Due to Edema, Faulty Nutrition or Interference by a Plastic Exudate*. Barach¹⁹ has called attention to the fact that in those conditions in which there is a

formation of pulmonary exudate or transudate, the presence of this material interferes with the gaseous exchange through the alveolar wall. This factor makes itself felt more especially in the areas of pneumonitis surrounding larger areas of consolidation.

(c) *Interference with Circulation in the Alveolar Walls.* Kline and Winternitz¹⁷ have shown that in the areas of gray hepatization there is little or no circulation of blood due to the formation of fibrin plugs within the capillaries, so-called fibrin capillary thrombi. With or without adequate alveolar capacity, if this vascular disturbance were extensive enough it would tend to hasten the blood flow through the remaining vascular channels, thereby shortening the duration of contact between blood and air, and decreasing the degree of oxygenation. Binger, Brow and Branch²⁰ have recently elaborated this point. Greene²¹ points out, however, that "the blood in the normal lung is in the pulmonary capillaries only about 1 second, yet the oxygen diffuses through into the venous blood fast enough to oxygenate it to arterial blood within the first two-fifths of this time. There is a variation among individuals, but a 60 per cent margin of safety in diffusion time exists. . . . In pulmonary inflammation, on the other hand, especially when associated with edema, the rate of absorption of oxygen may be greatly reduced." So that with an accelerated rate of blood flow in the presence of edema of the alveolar membranes, it is quite likely that this factor may contribute appreciably to the degree of anoxemia.

3. **INTRINSIC CHANGES IN THE CIRCULATING BLOOD.** Peabody, in 1913,²² attempted to show that the terminal symptoms and death in pneumonia are in part dependent on the changes produced in the hemoglobin molecule by the growth of the pneumococcus. This observation was based on experiments *in vitro*²³ which showed that the growth of pneumococcus on blood decreases the capacity of the blood for combining with oxygen. Further confirmation²⁴ was found in the changes of the blood of animals suffering with severe pneumococcus bacteremia, which changes were due to the conversion of hemoglobin into methemoglobin. Peabody²² then studied the blood of patients suffering from pneumonia and stated that "in the human body and in experimental animals death occurs before enough methemoglobin has been formed to be visible spectroscopically, but the falling off of the oxygen-combining power of the blood indicates that such a change is taking place." He was never able to demonstrate methemoglobin spectroscopically, however, and concludes that "while not attempting to assign a rôle that is all important to the changes in the blood, it would seem correct to consider that in many cases of pneumonia the terminal symptoms and death are in part produced in the hemoglobin molecule by the growth of the pneumococcus." It is not possible, therefore, at present to be able to assign a very considerable rôle to intrinsic changes in the blood in the production of anoxemia in pneumonia.

4. **INTRINSIC TISSUE DISTURBANCE.** There is little evidence in the literature upon which to base the belief that some intrinsic tissue disturbance is responsible to any considerable extent for the anoxemia of pneumonia. Stadie⁷ discusses the oxygen tension of the blood and tissue tension and gives a careful review of the available literature. About all that can be said is that the relations between normal and anoxic tissue function are not definitely established.

It might be argued that the existence of anoxemia in the course of pneumonia is of value in initiating certain defense reactions of the body in much the same way as fever is thought to do. In some ways such a position is not untenable in that, as Strughold²⁵ has recently shown, anoxemia in milder degrees leads to an increase in the minute volume flow of blood which effect would be distinctly beneficial to the pneumonic lung where the acute problem lies in furnishing adequate oxygen to the blood and in turn to the tissues. By increasing the minute volume flow a larger amount of oxygen, assuming adequate oxygen diffusion in the alveoli, would be delivered to the tissues. Serious complications arise in more advanced anoxemia, however, as shown by Schneider and Truesdell,²⁶ when there occurs a definite decrease in the minute volume of flow associated as a rule with dilatation of the heart. This early stimulating effect and later depressant action is apparently a direct action on the heart. As previously pointed out, Cannon and his coworkers^{11,12} have demonstrated the susceptibility of the cells in the vital brain centers to anoxemia.

It should be added that while all these various mechanisms probably play a part in the production of anoxemia in pneumonia, it appears certain that the chief causes, as pointed out by Peters and Van Slyke,¹⁰ are those related to the anatomic changes which retard the access of oxygen to the pulmonary blood.

Is There Danger of Overdosage of Oxygen? A careful discussion of this question involves the review of an extensive literature. Rather painstaking experimental work has been done on both man and animals but, unfortunately, considerable misinformation has arisen from it. In the first place, the older literature deals with work done on small laboratory animals, from which accurate conclusions cannot be drawn for man. As all of the work reported, furthermore, has been done on the normal organism, conclusions cannot be applied to the abnormal.

Smith, in 1899,²⁷ first discovered the poisonous effects of too much oxygen. He observed fatal pneumonia in rabbits exposed to over 80 per cent oxygen for 2 to 4 days. Benedict and Higgins,²⁸ in 1911, considered this question and give an excellent review of the literature. Man was used as the subject but the exposures to oxygen-rich mixtures were only of 10 or 15 minutes' duration. Karsner,²⁹ in 1915, further reviewed the literature and concluded,

from work done on rabbits, that atmospheres containing 80 to 96 per cent oxygen under normal barometric pressure produce in 1 or 2 days congestion, edema and, finally, a fibrinous bronchopneumonia. Barach,³⁰ in 1926, and Binger³¹ and his associates, more recently, confirmed these findings in rabbits. These conclusions, perhaps unconsciously, have been applied directly to man. It must be remembered, however, that blood fully saturated with oxygen cannot be expected to respond the same as blood markedly unsaturated; nor can abnormal alveolar membranes be expected to respond to oxygen as do normal ones.

The extensive literature on oxygen therapy contains no convincing evidence that any harmful effects attributable to oxygen itself have ever come from even continuous exposure of anoxemic or potentially anoxemic individuals to atmospheres of from 40 to 60 per cent oxygen for periods of as long as 2 months. This is a conservative statement to which there is only one exception, namely, conditions of chronic anoxemia as in chronic pulmonary disease and congenital heart disease where the factor of acclimatization has entered. These cases must be selected with care, as Boothby and Haines³² point out, for once they are in oxygen tents they frequently cannot be removed without causing an attack of acute "mountain sickness" which, in the debilitated condition in which these patients often are, proves fatal.

Indeed, there is a growing feeling that the administration of pure oxygen has definite advantages. Evans³³ has recently given a discussion of this subject from an experience arising from the administration of pure oxygen by means of a face mask to more than 100 cyanotic patients, for periods varying from 1 to 27 days, the administration being as nearly continuous as possible. He reports entirely satisfactory results with the development of no symptoms that might be attributed to an irritative action of the oxygen.

Actually the longest we have kept a patient under an oxygen tent practically continuously with resulting recovery is 22 days. The patient's pneumonia was complicated by bilateral empyema. Barach³⁴ reports having kept a patient, suffering with active bilateral pulmonary tuberculosis, under a tent for 7 months, with no evidence of irritation from the oxygen.

Dosage. At present it is felt that the optimum concentration of oxygen is between 40 and 60 per cent.³⁵ Any method which can supply a concentration above 30 per cent continuously and comfortably is of value. An oxygen concentration of less than 30 per cent rarely has any value; 30 to 35 per cent oxygen concentration generally lessens cyanosis and increases the arterial oxygen saturation. The nasal catheter method which is universally available will, when properly employed, furnish up to 35 per cent.³⁶ Its use should be continuous—day and night—if this be necessary to keep the patient comfortable. "Keep the finger nails pink," is a criterion

described by one clinician.³⁶ This is excellent but presupposes that cyanosis has developed. Stadie⁴ has shown that cyanosis of the finger nails and lips that just can be detected corresponds to approximately 10 per cent oxygen unsaturation. When cyanosis is definite the blood will be approximately 15 per cent unsaturated, and when marked, 20 to 30 per cent. Wineland and Waters³⁷ have recently attributed great importance to the pulse rate, this being, they assert, the most reliable single guide by which to judge benefit or failure from oxygen therapy. This point finds further confirmation in the work previously mentioned of Benedict and Higgins,²⁸ who found the lowering of the pulse rate to be the only factor in the metabolism of normal man, which shows consistent change in exposures to oxygen-rich atmospheres. In normal man the higher the percentage of oxygen breathed (up to 90 per cent), the lower the pulse. The fever may be uninfluenced because of the toxicity of the organism. The slowing of the pulse, however, occurs commonly, and is an indication that the part of the rapidity of the pulse due to the anoxemia is being relieved. Attention to the pulse, then, often is our best index. Our plan is to err on the side of safety and during the height of an infection, where experience has shown anoxemia is a factor, the patient is kept under the oxygen tent.

Indications for Oxygen Therapy. Medical Conditions. *Pneumonia.* Oxygen therapy is indicated in both lobar and bronchopneumonia. That oxygen unsaturation exists in pneumonia has been proven beyond doubt.^{4,6,8,44} That this unsaturation can be overcome by oxygen therapy has also been shown conclusively, both clinically as well as with confirmatory blood gas studies.^{7,19,39} The mass of reports in the literature from various workers all are in favor of early and continuous use of oxygen. The following statements summarize the effects of oxygen therapy in pneumonia which have been observed: (1) it gives greater comfort by making breathing easier; (2) it slows the pulse and, at times, the respiration and often lowers the temperature; (3) it increases the arterial oxygen saturation and relieves cyanosis; (4) finally, it frequently prolongs life until such time as the immunity mechanism is able to achieve recovery.

Even though precise statistical proof of the value of oxygen therapy is still lacking, these benefits cannot be ignored.

The first complete study of arterial and venous oxygen in pneumonia was made by Stadie⁴ in 1919. His contribution has been significant in that it has furnished a firm scientific foundation, now amply verified, for much of the speculation concerning oxygen therapy. He demonstrated that in all cyanotic pneumonia patients the blood was incompletely oxygenated. Furthermore, cases without cyanosis have an arterial unsaturation close to normal, which fact indicates that in pneumonia cyanosis is a reliable indication of the degree of anoxemia present. He showed that the anoxemia

of cyanotic pneumonia patients was entirely of the arterial or anoxic type and due to incomplete saturation of venous blood with oxygen in the lungs. It was not due to stagnation as the difference between the arterial and venous oxygen content, *i. e.*, oxygen consumption, was quite normal (3 to 5 volumes per cent).

A close correlation also was shown to exist between arterial unsaturation and mortality. In the fatal, as opposed to the non-fatal cases, the mean arterial and venous oxygen unsaturation respectively was 32 and 57 per cent, as against 13.9 and 36.3 per cent. Oxygen unsaturation of over 20 per cent as a rule was associated with a fatal outcome.

Binger⁶ has investigated more recently the correlation between anoxemia and mortality. His study calls attention to the comparatively few figures which have been published concerning the degree of arterial oxygen unsaturation which occurs in pneumonia, or the changes in saturation which follow oxygen therapy. His study presents the results of over 300 arterial punctures, and oxygen analyses made in 137 patients. By means of a simple frequency table he studied the percentage distribution of the various grades of anoxemia. There appeared to be a positive correlation between anoxemia and mortality. Moreover, the level of oxygen saturation in the arterial blood of a patient exposed to 40 per cent oxygen is of prognostic importance since the survivors usually reach a level of 90 per cent, while the fatal cases do so far less often. This is the first careful study presenting information obtained after exposures to oxygen-rich atmospheres that has appeared, and its value is vitiated by the size of the series studies.

It must be said, as Stadie⁷ points out, that not until the relation of function to oxygen tension is further elaborated can it be definitely said that anoxemia *per se* is a factor in the fatal outcome. It is fairly certain that a high degree of anoxemia in pneumonia is accompanied by a high mortality.

Heart Disease. Cardiac Decompensation. The indications for the use of oxygen therapy in heart disease are by no means clear. Many instances of its empirical use can be found, but not until recently has any intelligent concerted effort been made to study the problem clinically. Physiologists long ago uncovered many of the fundamental facts, but their clinical utilization, unfortunately, has been beset with grave difficulties. The complexity of cardio-respiratory physiology is apparent and even in the normal organism with the variation of one factor there occurs an elaborate shift in many others. These readjustments are further complicated by the presence of disease.

In heart disease the problem of the intelligent use of oxygen therapeutically is complicated by the fact that all three major types of anoxemia occur, and at times in the same patient. In pneumonia the contrast is apparent, as here anoxic anoxemia is

the major problem. The occurrence of anoxic anoxemia in heart failure was demonstrated first by Harrop⁸ and amply confirmed by Barach and Woodwell,¹⁹ Campbell, Hunt and Poulton,⁴¹ Rabinowitch,⁴² and others. That stagnant anoxemia occurs has also been proved by Means and Newburgh,⁴³ Lundsgaard,⁴⁴ Harrop,⁸ and Barach and Woodwell,⁴⁰ among others. The occurrence of anemic anoxemia in such heart conditions as subacute bacterial endocarditis and hypertension associated with chronic glomerulonephritis needs no elaboration.

It is encouraging that from efforts chiefly of Barach⁴⁵ and his associates⁴⁶ and Hamburger, *et al.*,⁴⁷ the clinical phases of this problem are being clarified. Barach⁴⁶ states, "The most interesting and striking effects of oxygen therapy in the cases of cardiac insufficiency, both those due to local disease of the heart itself and those in which heart failure appeared to be secondary to primary pulmonary disease, are: (1) relief of dyspnea and orthopnea; (2) elevation of the arterial carbon dioxid content and of the level of the carbon dioxid dissociation curves, and (3) diuresis."

In discussing the physiology of these effects Barach⁴⁶ says, "(1) The relief of dyspnea which frequently manifests itself within several hours after removal to oxygen-rich atmosphere indicates that oxygen want plays a decisive rôle in the production of cardiac dyspnea. It is evident (1) that the difficulties in oxygen absorption resulting from lung stiffening, decreased vital capacity and swollen alveolar membranes were overcome and (2) that the increased oxygen saturation of the pulmonary blood tends to diminish tissue acid accumulation. In the one case measured, the blood lactic acid rapidly returned to normal (22.6 mg. to 7 mg.). That the respiratory stimulus was thereby decreased is evidenced by the lowered pulmonary ventilation and that there was some decrease in general tissue acidity was suggested by the small but constant lowering of the arterial hydrogen-ion concentration which we observed."

In discussing the elevation of the arterial carbon dioxid content Barach⁴⁶ states, "When the anoxemia is relieved, there is a constant and marked rise in the carbon dioxid concentration of the blood with an even greater elimination of carbon dioxid per breath through the congested lung. Thus, in one of the cases of congestive failure, the carbon dioxid content of the arterial blood rose from 38.4 to 69.9 volumes per cent in 4 days. It appears, therefore, likely that the elevation in carbon dioxid level in the blood is an adaptive change which is readily accomplished if sufficient oxygen is supplied to maintain normal metabolic activity. Also, lactic acid accumulation disappears when anoxemia is relieved. It seems probable that base to retain carbon dioxid is in part derived from the blood lactates in this man. A decrease in pulmonary ventilation follows with a lessened sense of pulmonary effort, and therefore relief of dyspnea."

Knowledge concerning the mechanism of the diuresis which occurred is incomplete. Barach⁴⁶ merely states that, "oxygen therapy resulted in an improved state of the circulation which would tend to relieve the edema due to stasis as well as relieve the passively congested glomerular membranes. In so far as the tissue cells of the body are altered in their permeability due to anoxemia, an increased oxygen supply would otherwise be beneficial."

It would seem, therefore, in the presence of low arterial oxygen saturation, that while an old, damaged heart cannot be repaired fully by oxygen, nevertheless much of the acute distress so often seen in cardiac decompensation may be avoided to a large extent. During the time that digitalis, diuretics and morphin are taking to produce their effects it may be possible to put these patients in relative comfort by the use of oxygen.

Coronary Thrombosis. Levy and Barach⁴⁸ report their experience with the administration of oxygen by means of a tent to 4 patients suffering with coronary thrombosis. They state that their experience would indicate that anoxemia may play a crucial rôle in determining the outcome after coronary thrombosis. There is first of all a state of shock due to a sudden interference with the blood supply of the heart. If the resulting area of myocardial infarction is large, evidence of congestive heart failure swiftly ensues. The heart action becomes weak, sometimes irregular and rapid, with the characteristic muffling and shortening of the mitral first sound. The blood pressure falls sharply. Cyanosis appears and moist râles are heard at the base of the lungs. The breathing is rapid and difficult. Acute oxygen want is present, manifested by both arterial and venous anoxemia. Employment of oxygen therapy in a concentration of from 40 to 60 per cent may and has aided in maintaining an adequate oxygen supply to the tissues of the body until the heart has had an opportunity to recover from its acute functional disturbance.

In the experience of Barach there are cases in which the administration of oxygen will prolong life and result in recovery from the acute episode. Two out of 3 cases of coronary arteriosclerosis with chronic heart pain, reported by Barach,⁴⁹ have been relieved from exposures to an atmosphere of 50 per cent oxygen. These cases have been followed for approximately 6 months. Barach⁴⁶ states that it is not possible at present to explain entirely the mechanism by which the relief of the pain occurs. The following factors play a part. "In the first place, the inhalation of 50 per cent oxygen in normal men we have found capable of raising the arterial oxygen saturation from 95 to 99 per cent. In one of the cases of coronary arteriosclerosis, which we measured, the arterial oxygen saturation was raised from 94 to 99 per cent. Although this represents a small increase in per cent saturation, it indicates a considerable rise in the tension or partial pressure of oxygen available to the tissues

(because of the shape of the oxygen dissociation curve) and provides therefore a possible explanation for relief of local anoxemia in the heart muscles. The inhalation of high concentrations of oxygen causes the normal heart to beat at a slower rate,²⁸ and affects more markedly the heart in cardiac insufficiency, which suggests^{40,50} a lessened strain due to a greater oxygen supply."

OXYGEN THERAPY IN ALLIED CONDITIONS. Less frequent is the indication for oxygen therapy in other medical conditions. Its use has been reported, however, in bronchitis^{33,51} and asthma, hyperthyroidism,^{52,53} asphyxia,⁵⁴ asphyxia of the newborn,^{56,56,57,58} influenza,³³ and certain neuropsychiatric conditions.^{49,59,60} Reports of the use of oxygen in other conditions such as epilepsy, chronic arthritis, sepsis, diabetes mellitus, burns and hypertension have appeared, but as yet conclusions cannot be drawn.

Surgical Conditions. The most interesting work in the use of oxygen in surgical conditions has perhaps been done in The Mayo Clinic (Judd and Passalacqua⁶¹). Boothby and Haines⁶² early convinced this group of the advantages of oxygen therapy. Judd states that there are certain types of operations in which pulmonary complications are more likely to follow, such as interventions in the upper organs of digestion for cancer of the stomach, ulcer, gastrojejunal fistula, biliary obstruction and operations on the pancreas. Effort has been directed toward the development of some hygienic or therapeutic method that might minimize the possibility of post-operative pneumonia. It appears to them that since the use of the oxygen tent has been instituted they do not have in their service the incidence of pneumonia that they had at other times.

In this particular paper⁶¹ 180 unselected cases are reported in which oxygen without CO₂ was administered under one of three sets of circumstances: (1) as a prophylactic measure against pneumonia immediately after operation; (2) as soon as the signs and symptoms of pulmonary congestion were recognized clinically; (3) after the classical signs of pneumonia were present. In the first group were 105 among whom pneumonia did not occur. The same results were evident in the second group of 43 with pulmonary congestion. In the third group not one casualty was registered and the progress of the disease apparently was influenced by the use of oxygen. It seems likely, however, that carbon dioxid will supplant oxygen to a large extent in the treatment of the postoperative pulmonary complications.

The Use of Carbon Dioxid With Oxygen in the Treatment of Pneumonia. Few topics are of more vital interest at present than the use of carbon dioxid in the treatment of pneumonia. Thoughtful workers with oxygen tents have frequently expressed the opinion that the absorption of carbon dioxid out of the system by the use of soda lime, aside from being expensive, was dangerous because it tended to remove the normal stimulant to respiration, and in

case of accidental obstruction of the oxygen tube would remove any possibility of warning. The recent trends toward elimination of soda lime⁶³ are efforts toward the elimination of these defects.

The function of carbon dioxid in the treatment of pneumonia has been elaborated most brilliantly by Y. Henderson and his coworkers, and many facts have been adduced which throw an entirely new light on our traditional ideas. Henderson⁶⁵ makes the interesting statement that "it is a significant fact that no one has yet reported the cure of an experimentally induced pneumonia by means of a vaccine, a serum or an antitoxin. On the other hand, experimental pneumococcic pneumonia has been cured with carbon dioxide." Their demonstration of the specific effect of carbon dioxid in preventing secondary pneumonia is fairly well known.⁶⁴ Now Henderson⁶⁵ feels that in all pneumonias by the use of carbogen, a convenient term for mixtures of oxygen and carbon dioxid, morphin, or other narcotic drugs may be used more freely to counteract excitement and restlessness. The stimulus to respiration afforded by the carbon dioxid tends to counteract the depression of breathing which such drugs otherwise induce. The value of morphin in pneumonia is established but individual experiences color our enthusiasms. In England there is a general belief that morphin affords fundamental and not merely symptomatic benefit in pneumonia. Henderson suggests the following rational explanation for this belief, "The principal physiologic effect of morphine . . . is to raise the threshold of the respiratory center for carbon dioxide. This means that respiration under morphine automatically decreases the volume of air breathed per minute to such an extent that, as the amount of carbon dioxide in the body is unaltered, a much higher concentration of carbon dioxide is maintained in the lungs even when there is no carbon dioxide in the inspired air. When, in addition, the patient breathes air containing an appreciable amount of carbon dioxide, the concentration increases to amounts corresponding to or somewhat exceeding those in the lungs during moderate physical exercise, but without its hyperpnea."

By means of this increase in the alveolar carbon dioxide content, the bactericidal action of carbonic acid upon the pneumococcus and the promotion of solution in the pneumonic exudate by carbonic acid may make itself felt. Lord^{66,67} has called attention to these two probable actions of carbonic acid, but in order for these effects to be manifested carbon dioxid inhalation needs the assistance of morphin or some other respiratory depressant drug.

Kline and Winternitz¹⁷ were able to show experimentally that "the presence of fibrin plugs throughout the capillary bed of the pneumonic lung interferes greatly with the penetration of such a diffusible substance as trypan blue, when this drug is injected intravenously, but the exudate offers no serious obstruction to the penetration of the dye into the alveoli when it is injected intrabronchi-

ally." This suggested to them a reason for the restricted action of immune serum in pneumonia, and further suggested a basis for the intrabronchial treatment of pneumonia. This is the approach which carbon dioxid therapy uses, and the soundness of it is further strengthened by these observations.

In conclusion, it can be seen that the interest in oxygen therapy has been of considerable magnitude during the past decade. It seems quite certain that oxygen therapy has definitely established itself in our therapeutic armamentarium. In those conditions associated with easily recognized anoxemia and in the more obscure conditions as they are recognized, the use of oxygen must find its place. Our knowledge must increase greatly before we can speak upon this subject with anything like finality. The time is at hand, however, when oxygen must be given a trial in serious heart and pulmonary conditions. That carbon dioxid will supplement oxygen seems possible, and a valuable supplement it bids fair to be.

BIBLIOGRAPHY.

1. Haldane, J. S.: Respiration, New Haven, Yale Univ. Press, 1922; London, Humphrey Milford, Oxford Univ. Press.
2. Hürtner: Deutsch. Arch. f. klin. Med., 1912, 188, 1.
3. Lundsgaard, C.: J. Biol. Chem., 1918, 33, 133.
4. Stadie, W. C.: J. Exp. Med., 1919, 30, 215.
5. Van Slyke, D. D.: J. Biol. Chem., 1918, 28, 127.
6. Binger, C. A. L.: J. Clin. Invest., 1928, 6, 203.
7. Stadie, W. C.: J. Exp. Med., 1922, 35, 337.
8. Harrop, G. A., Jr.: J. Exp. Med., 1919, 30, 240.
9. Harrison, T. R., and Pileher, C.: J. Clin. Invest., 1930, 8, 259.
10. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. I, Interpretations, Baltimore, The Williams & Wilkins Company, 1931, pp. 592 *et seq.*
11. Cannon, W. B., and Haskins, R. G.: Am. J. Physiol., 1911, 29, 274.
12. Cannon, W. B., and Burket, R.: Am. J. Physiol., 1913, 32, 347.
13. Palthé, P. M. van W.: Deutsch. Ztschr. f. Nervenhe., 1926, 92, 79.
14. Greene, C. W., and Gilbert, N. C.: Am. J. Physiol., 1922, 60, 155.
15. Meakins, J. C.: Arch. Int. Med., 1920, 25, 1.
16. Binger, C. A. L., and Davis, J. S., Jr.: J. Clin. Invest., 1928, 6, 171.
17. Kline, B. S., and Winternitz, M. C.: J. Exp. Med., 1915, 21, 311.
18. Gross, L.: Canadian Med. Assn. J., 1919, 9, 632.
19. Barach, A. L., and Woodwell, M. N.: Arch. Int. Med., 1921, 28, 415.
20. Binger, C. A. L., Brow, G. R., and Branch, A.: J. Clin. Invest., 1924, 1, 155.
21. Greene, C. W.: J. Am. Med. Assn., 1925, 85, 645.
22. Peabody, F. W.: J. Exp. Med., 1913, 18, 7.
23. Butterfield, G. E., and Peabody, F. W.: J. Exp. Med., 1913, 17, 587.
24. Peabody, F. W.: J. Exp. Med., 1913, 17, 1.
25. Strughold, H.: Am. J. Physiol., 1930, 94, 641.
26. Schneider, E. C., and Truesdell, D.: Am. J. Physiol., 1924, 71, 90.
27. Smith, J. S.: J. Physiol., 1899, 24, 19.
28. Benedict, F. G., and Higgins, H. L.: Am. J. Physiol., 1911, 28, 1.
29. Karsner, H. J.: J. Exp. Med., 1916, 23, 149.
30. Barach, A. L.: Am. Rev. Tuberc., 1926, 13, 293.
31. Binger, C. A. L., Faulkner, J. M., and Moore, R. L.: J. Exp. Med., 1927, 45, 849.
32. Boothby, W. M., and Haines, S. F.: J. Am. Med. Assn., 1928, 90, 372.
33. Evans, J. H.: Canadian Med. Assn. J., 1930, 22, 518.
34. Barach, A. L., and Richards, D. W.: To be published.
35. Barach, A. L.: Arch. Int. Med., 1926, 37, 188.
36. Guedel, A. E.: J. Am. Med. Assn., 1925, 84, 1490.
37. Wineland, A. J., and Waters, R. M.: Arch. Surg., 1931, 22, 67.

38. Barach, A. L.: J. Am. Med. Assn., 1929, 93, 1550.
39. Meakins, J. C.: J. Path. and Bact., 1921, 24, 79.
40. Barach, A. L., and Woodwell, M. N.: Arch. Int. Med., 1921, 28, 367.
41. Campbell, J. M. H., Hunt, G. H., and Poulton, E. P.: J. Path. and Bact., 1923, 26, 234.
42. Rabinowitch, I. M.: Arch. Int. Med., 1925, 36, 239.
43. Means, J. H., and Newburgh, L. H.: Trans. Assn. Am. Phys., 1915, 30, 51.
44. Lundsgaard, C.: J. Exp. Med., 1918, 27, 179.
45. Barach, A. L., and Richards, D. W., Jr.: Arch. Int. Med., 1931, 48, 325.
46. Barach, A. L.: Ann. Int. Med., 1931, 5, 428.
47. Hamburger, W. W., Katz, L. N., Cohn, D. J., and Rubinfeld, S. H.: J. Am. Med. Assn., 1932, 94, 1363.
48. Levy, R. L., and Barach, A. L.: J. Am. Med. Assn., 1930, 94, 1363.
49. Barach, A. L.: Anesth. and Analg., 1932, p. 71.
50. Barach, A. L., Dickinson, R. W., Milberato, A. I., and Levy, R. L.: Proc. Soc. Exp. Biol. and Med., 1930, 27, 308.
51. Campbell, J. M. H., and Poulton, E. P.: Quart. J. Med., 1926, 20, 27.
52. Boothby, W. M., and Haines, S. F.: Am. J. Surg., 1929, 6, 1.
53. Pemberton, J. DeJ.: N. Y. State J. Med., 1928, 28, 256.
54. Henderson, Y., and Haggard, H. W.: J. Am. Med. Assn., 1921, 77, 1065.
55. Coryllos, P. N.: Am. J. Obst. and Gynec., 1931, 21, 513.
56. Murphy, D. P., Wilson, R. B., and Bowman, J. E.: Am. J. Obst. and Gynec., 1931, 21, 528.
57. Flagg, P. J.: Am. J. Obst. and Gynec., 1931, 21, 537.
58. Henderson, Y.: Am. J. Obst. and Gynec., 1931, 21, 542.
59. Solomon, H. C., Kaufman, M. R., and D'Elseaux, F.: Am. J. Psychiat., 1931, 10, 761.
60. Seegal, L., and Hinsie, L. E.: AM. J. MED. SCI., 1926, 171, 727.
61. Judd, E. S., and Passalacqua, L. A.: Clin. North America, (Feb.) 1929, Surg., 9, 13.
62. Boothby, W. M., and Haines, S. F.: Trans. Am. Phys., 1927, 42, 287.
63. Rosenbluth, M. D., and Block, M.: J. Am. Med. Assn., 1932, 98, 396.
64. Henderson, Y., Haggard, H. W., Coryllos, P. N., and Bernbaum, G. L., Jr.: Arch. Int. Med., 1930, 45, 72.
65. Henderson, Y.: New Eng. J. Med., 1932, 206, 151.
66. Lord, F. T.: J. Exp. Med., 1919, 30, 379.
67. Lord, F. T., and Nye, N. N.: J. Exp. Med., 1919, 30, 389.

LYSOZYME IN SALIVA.

BY NICHOLAS KOPELOFF, PH.D.,

RESEARCH ASSOCIATE IN BACTERIOLOGY,

AND

MEYER M. HARRIS, M.D.,

RESEARCH ASSOCIATE IN INTERNAL MEDICINE,

AND

BARBARA MCGINN, B.A.,

LABORATORY TECHNICIAN,
NEW YORK.

(From the Departments of Bacteriology and Internal Medicine, Psychiatric Institute and Hospital.)

THE interesting researches of Fleming¹ established the presence of lysozyme in human saliva. This lytic agent is so potent that when saliva is diluted 1 to 300 *Micrococcus lysodeikticus* is com-

pletely dissolved in 1 hour at 45° C. Because of the possible rôle of focal infection in psychotic states² Penrose³ sought "to discover whether any corresponding alteration could be observed in the lysozyme content of the saliva of psychotics as compared with the normal." His tests on 26 psychotic patients and 6 normal controls are summarized as follows: "The figures quoted suggest that there is no significant difference between the normals, mental defectives and cases of dementia præcox with regard to the lysozyme content of saliva, but that in organic psychoses, such as G. P. I. and Parkinsonism (general paralysis and postencephalitic Parkinsonism) the concentration is much diminished."

In view of these findings we undertook an investigation of the lysozyme content of the saliva of 14 postencephalitic patients, 2 general paralytics, 1 acute encephalitic, and 14 laboratory workers of the Psychiatric Institute who graciously volunteered to serve as controls. Through the kind coöperation of Miss Frances J. McClellan, of the Neurologic Institute, we were able to obtain specimens of saliva from the postencephalitic patients.

Procedure. Specimens of saliva were centrifuged for 5 minutes at medium speed immediately after collection and 1 cc. used for the original dilution. Further dilutions were made with physiologic saline. One cubic centimeter of an 18-hour growth of *Micrococcus lysodeikticus* (averaging 5,000,000,000 organisms) to 9 cc. of diluted saliva yielded the final desired concentration. We are indebted to Prof. Alexander Fleming for very generously supplying us with the original culture. The saliva culture mixture was incubated (within 10 minutes) at 45° C. for 1 hour together with controls of the culture in saline. Seven-eighths or more lysis was considered positive. In order to attain objective accuracy, in our later studies, standard 7/8 tubes were prepared by adding 8.75 cc. of diluent to 1.25 cc. of a 1 to 10 suspension of *Micrococcus lysodeikticus*. Also when these standard tubes were employed we followed Penrose's suggestion of using equal parts of normal saline and isotonic phosphate buffer solution instead of normal saline so as to obviate any adverse influences of the saliva on the hydrogen-ion concentration. The diluting fluid was, therefore, made up of equal parts of 0.14 molar NaCl and phosphate mixture (2 parts 0.14 molar KH_2PO_4 added to 8 parts of 0.14 molar $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) yielding, according to Sorenson, a final pH of 7.4. Our data in Table 1 have been recorded under two headings—"Preliminary Technique" where physiologic saline was used as a diluent and 7/8 lysis judged by inspection, and "Modified Technique" where a buffered solution of pH 7.4 was employed as a diluent and the lysis was judged by comparison with a standard tube. Readings of 5/8 lysis by the "modified technique" are also included.

Results. From Table 1 it will be seen that of the 14 postencephalitic patients 12 showed lysis at least once in a dilution of 1/300 and 2 in 1/100 with the "preliminary technique."* Of the 14 normal controls 12 showed lysis at least once in a dilution of 1/300 and 1 each in dilutions of 1/100 and 1/200. In other words the results

* Six patients and 4 controls, all of whom showed lysis in a dilution of 1/300, were omitted from Table 1 since only a single specimen was taken.

TABLE 1.—LYTIC ACTION OF SALIVA ON *MICROCOCCLUS LYSODEIKTICUS*.

Cases.	Preliminary technique (7/8 lysis).							Modified technique (7/8 lysis).							5/8 lysis.			
	Dec. 8, †	Dec. 12.	Dec. 15.	Jan. 5.	Jan. 7.	Jan. 12.	Jan. 14.	Mar. 4.	Mar. 16.	June 8.	June 15.	July 9.	Mar. 4.	June 8.	June 15.	July 9.	July 13.	
Encephalitis.																		
Hr . .	1/300 +	...	1/1200 +	1/100 +	1/50 -	1/50 +	1/100 -	...	
Gg . .	1/300 +	...	1/100 +	1/100 +	...	1/500 +	1/50 -	1/50 -	
Hr . .	1/300 +	...	1/1000 -	1/1000 +	1/100 -	1/200 +	1/300 -	...	
Gil . .	1/300 +	...	1/100 +	1/50 -	1/100 +	1/200 -	...	
Wr . .	1/300 +	...	1/100 +	1/100 +	1/100 -	1/50 -	1/200 +	1/300 -	1/300 +	
Sn . .	1/300 +	...	1/800 -	1/100 +	1/25 -	1/200 +	1/300 -	...	
Ar*	1/100 -	1/300 -	...	1/100 -	1/100 -	1/50 -	...	1/25 -	1/200 +	1/300 -	
As	1/100 +	
Gc	1/300 -	
General paralytic.																		
Rh . .	1/100 +	
Sn . .	1/200 +	1/300 +	
Normals.																		
Kf . .	1/300 +	1/200 +	1/1000 +	1/100 -	1/300 +	1/100 +	1/100 -	1/100 -	1/50 -	1/50 -	1/25 -	1/25 -	1/100 +	1/25 +	1/100 +	1/200 -	...	
Hs . .	1/100 +	...	1/1000 +	1/100 -	1/300 -	1/100 -	1/100 -	1/100 -	1/50 -	1/25 -	1/50 -	1/25 -	1/100 +	1/50 +	1/25 +	1/50 -	1/100 +	
Mn . .	1/300 +	1/300 +	1/1000 +	1/100 +	1/300 +	1/100 +	1/100 -	1/100 -	1/50 -	1/25 -	1/25 -	1/25 -	1/200 -	1/50 +	1/25 +	1/50 -	1/200 -	
Bn . .	1/100 +	1/300 +	1/100 -	1/100 -	1/500 -	1/100 -	1/100 -	1/100 -	1/50 -	1/25 -	1/50 -	1/25 -	1/200 -	1/25 +	1/200 -	
Hp . .	1/300 +	...	1/100 -	1/25 -	1/25 +	1/50 -	...	
Sr . .	1/300 +	...	1/100 -	1/25 -	1/50 -	
Un . .	1/300 +	...	1/1000 +	1/25 -	1/200 +	1/300 -	...	
Wr	1/1200 -	1/25 -	1/300 -	
Ca . .	1/300 +	...	1/100 -	
Wl . .	1/300 +	...	1/100 -	

* Acute encephalitis.

† On this date 6 other cases of encephalitis and 3 normals showed 7/8 lysis at 1/300 +.

were the same for postencephalitic patients and normals. With the "modified technique" neither postencephalitic patients nor normals showed 7/8 lysis (in dilutions of 1/25 or upward). If 5/8 lysis is employed as the criterion, then of 6 postencephalitic patients studied 1 showed lysis in 1/300, 2 in 1/200, 1 in 1/100 and 1 in 1/50. Of the 5 normals 1 showed lysis in 1/200, 2 in 1/100 and 2 in 1/50. Again this indicates no lack of lysozyme content in the saliva of postencephalitic patients as compared with normals.

It will be observed that there is considerable variation in the lysozyme content of any individual on repeated tests. Thus Gg, on December 8, 1930, showed lysis in 1/300, on December 15, 1/800, on January 8, 1931, lysis in 1/100 and on January 12 lysis in 1/500 with the "preliminary technique" but failed to show lysis in 1/50 on June 15, 1931 with the "modified technique." The experimental error is obviously too large to permit of any generalizations differentiating postencephalitic patients from normals on this basis.

There is always a possibility in dealing with a bacteriologic test that variations in the culture may be responsible for unaccountable discrepancies. Consequently we investigated the influence of time of incubation of *Micrococcus lysodeikticus* before use, the age of the culture and the medium upon which it was grown.

TABLE 2.—ACTIVITY OF *MICROCOCCUS LYSODEIKTICUS* IN BUFFERED POWDERED EGG ALBUMEN SOLUTION.

Date, 1931.	Albumen.	"Old culture."		"New culture."	
		7/8 lysis.	5/8 lysis.	7/8 lysis.	5/8 lysis.
Mar. 20	A	1/10,000 +			
April 16	A	1/10,000 +			
	B	1/10,000 +			
20	B	1/10,000 +	1/19,000 +	1/10,000 +	1/19,000 +
		1/13,000 -	1/21,000 -	1/13,000 -	1/21,000 -
June 8	B	1/10,000 +	1/15,000 +		
		1/12,000 -	1/20,000 -		
11	B	1/10,000 +	1/15,000 +
				1/12,000 -	1/20,000 -
15	B	1/8,000 +	1/15,000 +
				1/10,000 -	1/20,000 -
15	C	1/10,000 +	1/25,000 +
				1/12,000 -	
26	C	1/8,000 +	1/15,000 +
				1/10,000 -	

The first culture of *Micrococcus lysodeikticus* grown on casein digest agar was incubated for 18 hours on casein digest agar, and from this a saline suspension was made which had a microscopic count of 6,500,000,000 organisms per cc. The second culture was incubated for 16 hours and had a count of 5,000,000,000 per cc.

Thereafter we employed 48-hour growths made up to a nephelometric standard to yield a final count of 5,000,000,000 organisms per cc. In this way the number of *Micrococcus lysodeikticus* used at each test was constant and of the same age. The transfers were made serially from the culture sent us originally by Professor Fleming. Thinking that perhaps continued transfers had weakened or strengthened the culture, we started new transfers in April from a duplicate which had been ice-boxed since November. This change had no appreciable influence on our results. The cultures are labeled "old" and "new," respectively, in Table 2.

As a final check on the activity of the culture, powdered egg albumen which is known to have lytic properties was made up with buffered solution, filtered, and toluene added as a preservative. Repeated tests with samples A, B and C yielded uniform results which are recorded in Table 2.

In an attempt to make the "new" culture more susceptible to lysis it was grown on beef extract agar. In Table 3 are recorded the results of tests with buffered powdered egg albumen solution.

TABLE 3.—INFLUENCE OF MEDIUM ON LYSIS OF *MICROCoccus* *LYSODEIKTICUS* BY EGG ALBUMEN.

Agar medium.	Number of transfers.	7/8 lysis.	5/8 lysis.
Casein digest	15	1/8,000 + 1/10,000 -	1/15,000 + 1/20,000 -
Beef extract	5	1/10,000 + 1/12,000 -	1/30,000 + 1/40,000 -
Beef extract	12	1/15,000 + 1/17,000 -	1/30,000 + 1/40,000 -
Beef extract	14	1/17,000 + 1/20,000 -	1/30,000 + 1/40,000 -

From Table 3 it will be seen that susceptibility to lysis was somewhat increased by growing the culture on beef extract agar instead of casein digest agar. No striking change in colony formation was observed. One might speculate on the possibility of increasing the susceptibility of *Micrococcus lysodeikticus* still further by adaptation to more appropriate media. However, from the studies just described it may be inferred that *Micrococcus lysodeikticus* is a stable culture which does not vary markedly under different conditions of growth, and that it is therefore admirably suited for the purpose which Fleming suggested, namely, a measure of the lytic principle present in human secretions.

Summary. 1. Human saliva contains lysozyme, the activity of which may be measured by the dissolution of *Micrococcus lysodeikticus* as described by Fleming.¹

2. No differences could be discerned between the lysozyme content of postencephalitic patients and normals when accurate standards were employed. This is contrary to the findings of Penrose.²

3. Neither the age of the culture nor the incubation period within the limits indicated have any significant influence on the test.

4. The composition of the medium, however, does exert an appreciable influence on the susceptibility of *Micrococcus lysodeikticus* to lysis.

BIBLIOGRAPHY.

1. Fleming, A.: Lysozyme: A Bacteriolytic Ferment Found Normally in Tissues and Secretions, *Lancet*, 1929, 1, 217.
2. Kopeloff, N., and Kirby, G. H.: Focal Infection and Mental Disease, *Am. J. Psychiat.*, 1923, 3, 149.
3. Penrose, L. S.: The Lysozyme Content of Saliva in Psychotics, *Lancet*, 1930, 2, 689.

A STUDY OF "IRON VOLUME INDEX" OF THE BLOOD AND ITS SIGNIFICANCE IN THE TREATMENT OF ANEMIA.

BY CARL REICH, A.B., M.D.,

ASSISTANT ADJUNCT PHYSICIAN AND ATTENDING, HEMATOLOGY CLINIC,

AND

VERA G. TIEDEMANN, A.B.,

TECHNICAL ASSISTANT,
NEW YORK.

(From the Medical Service of Dr. Otto Hensel, Lenox Hill Hospital.)

IN his "De Ferrearum Particularum Sede in Sanguine," published in 1746, Menghini¹ first called attention to the presence of iron in the blood. Since this time many papers have been written on the subject, dealing, however, almost entirely with the methods for determining the iron, the quantities in which it is present in the blood and the correlation between the iron and the hemoglobin. An excellent review of this literature may be found in an article of recent date by Murphy, Lynch and Howard.² These investigators went a step further and established an iron index, the purpose of which was to aid in differentiating and treating the various types of anemia. This index was calculated by dividing the milligrams of iron per 100 cc. of whole blood by the red blood count expressed in millions per cubic millimeter. The average iron index was 8.46, and Murphy and his coworkers considered it analogous to the well known color index, only more reliable.

Recently, however, Haden,³ Wintrobe,⁴ Osgood,⁵ and others have emphasized the importance of determining the size of the red blood cell and of correlating this information with other data such as the number of the red blood cells and their hemoglobin content. These determinations are known as the volume index and the saturation index. The volume index expresses the relationship between the cell volume and the number of cells, while the saturation index

NORMALS.

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.D.C., millions vol. per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Satura- tion index.	Iron volume index.	Average vol. of erythro- cyte, cubic microns.	Average Hb. per erythro- cyte, gm. × 10 ⁻ⁿ Hb.	Average iron per erythro- cyte, mg. × 10 ⁻ⁿ Ic	Hb. Ic
1.	M	35	Chronic cardiac valvular disease	13.7	88	4.5	41	40.0	0.99	0.98	0.97	91.1	1.24	3.64	340
2.	M	47	Tuberc	14.8	96	5.1	44	44.1	0.93	1.00	1.00	86.2	1.27	3.80	354
3.	M	37	Gastric neurosis	15.6	100	5.3	48	48.5	0.98	0.95	1.00	90.5	1.41	4.38	321
4.	M	17	Chronic tonsillitis	13.5	87	4.6	42	43.5	0.99	0.95	1.00	91.3	1.23	3.97	309
5.	M	21	Gastric neurosis	16.6	107	5.8	49	50.0	0.91	1.00	1.00	84.4	1.40	4.22	326
6.	M	60	Acute bronchitis	14.0	90	4.5	40	42.0	0.96	0.96	1.00	88.8	1.24	3.61	343
7.	M	53	Angina pectoris	13.5	87	4.4	40	41.0	0.98	1.00	1.00	90.9	1.22	3.72	327
8.	M	45	Gastric neurosis	14.0	90	4.6	41	42.1	0.97	0.98	1.00	89.1	1.24	3.75	330
9.	M	31	Blood donor	15.6	100	5.0	45	43.0	0.97	1.00	0.95	90.0	1.40	3.87	361
10.	M	32	Pneumonia	13.2	85	4.6	40	41.0	0.94	0.97	1.00	87.0	1.14	3.56	320
11.	M	46	Cardiac neurosis	14.0	90	4.6	42	41.7	0.99	0.98	0.99	91.3	1.27	3.80	334
12.	M	58	Gastric neurosis	14.8	95	4.9	45	46.3	0.98	1.00	0.95	91.7	1.35	4.24	318
13.	M	33	Sacroileal disease	12.6	81	4.2	38	40.1	0.98	0.98	1.00	90.4	1.13	3.62	359
14.	M	22	Cut tendons of hand	14.0	90	4.7	42	43.1	0.97	0.98	1.00	85.1	1.19	3.60	325
15.	M	25	Cardiac neurosis	15.6	100	5.0	46	48.7	1.00	1.00	1.00	82.0	1.43	4.48	319
16.	M	30	Gastric neurosis	14.0	90	4.7	42	42.0	0.99	0.98	1.00	89.3	1.25	3.75	333
17.	M	40	Laceration of hand	14.3	92	4.8	44	46.0	0.99	0.92	1.00	91.6	1.30	4.21	308
18.	M	31	Kidney stone	14.0	90	4.7	42	42.2	0.97	0.98	1.00	89.3	1.25	3.76	332
19.	M	50	Contusion of leg	13.8	89	4.5	41	42.5	0.99	0.99	0.96	91.0	1.25	3.86	323
20.	M	20	Grippe	13.7	88	4.6	40	36.8	0.99	1.00	0.92	91.1	1.24	3.35	370
21.	M	54	Diabetes	14.0	90	4.7	42	40.4	0.97	0.98	0.96	89.3	1.25	3.60	347
22.	M	40	Ulcerative colitis	14.8	95	5.4	48	40.4	0.97	0.91	0.84	88.8	1.31	3.58	365
23.	F	68	Chronic myocarditis	12.4	80	4.2	36	38.8	0.93	1.00	1.00	85.7	1.06	3.42	309
24.	F	40	Chronic appendicitis	12.7	82	4.4	40	43.5	0.98	0.94	1.00	90.9	1.15	3.95	291
25.	F	32	Gastric neurosis	12.4	80	4.0	36	38.1	0.97	1.00	1.00	90.0	1.16	3.42	339
26.	F	31	Chronic appendicitis, operation	14.8	95	4.9	45	42.5	0.99	0.97	0.91	91.8	1.35	3.90	343
27.	F	47	Auto appendicitis, operation	13.2	85	4.5	40	37.4	0.96	0.97	0.93	88.8	1.17	3.31	353
28.	F	30	Chronic salpingitis, Wass. 4+	13.2	85	4.6	40	36.4	0.94	0.97	0.91	86.9	1.14	3.10	360
29.	F	55	Chronic alcoholism	13.5	87	4.7	43	43.2	0.99	0.94	1.00	91.4	1.23	3.94	310
30.	F	40	Chronic salpingitis	12.4	80	4.3	39	42.5	0.98	0.98	1.00	90.7	1.12	3.85	290
31.	F	38	Chronic arthritis	14.0	90	4.9	42	44.4	0.93	0.98	1.00	85.7	1.20	3.80	316
32.	F	65	Chronic myocarditis	15.6	100	5.0	45	42.7	0.99	1.00	0.95	90.0	1.40	3.84	364
33.	F	38	Chronic arthritis	14.1	91	4.7	43	37.4	1.00	0.97	0.87	91.4	1.28	3.41	375
34.	F	39	Sciatica	14.3	92	4.6	44	45.0	0.95	0.96	1.00	95.6	1.36	4.30	316

35	F	64	Chronic arthritis	15.6	100	5.0	45	45.0	0.98	1.00	1.00	90.0	1.40	4.05	345
36	F	23	Influenza	12.9	83	4.4	40	42.5	0.99	0.95	1.00	90.9	1.17	3.86	303
37	F	25	Catarrhal jaundice	13.1	84	4.5	41	43.0	0.99	0.94	1.00	91.1	1.19	3.91	304
38	F	49	Exophthalmic goiter	12.6	81	4.4	41	40.5	1.00	0.90	1.00	93.1	1.17	3.77	300
39	F	51	Cellulitis of arm	14.1	91	4.7	43	43.5	0.99	0.97	1.00	91.4	1.27	3.87	302
40	F	35	Glandular fever	13.4	86	4.6	40	40.7	0.99	0.98	1.00	86.9	1.16	3.53	328
41	F	50	Chronic arthritis	15.6	100	5.0	44	47.6	0.95	1.00	1.00	88.8	1.38	4.21	325
42	F	60	Arteriosclerosis	14.0	90	4.5	41	43.5	0.99	1.00	1.00	91.3	1.27	3.97	319
43	F	30	Chronic bronchitis	14.0	90	4.8	41	42.5	0.92	1.00	1.00	85.4	1.19	3.52	338
44	F	42	Chronic bronchitis	12.4	80	4.2	37	40.7	0.95	0.99	1.00	88.0	1.09	3.58	304
45	F	40	Chronic arthritis	14.0	90	4.8	42	43.4	0.92	0.98	1.00	87.4	1.22	3.79	321

ANEMIAS (IRON VOLUME INDEX 1).

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	Hb., %.	R.B.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Satura- tion index.	Iron volume index.	Average vol. of erythro- cyte, cubic microns.	Average Hb. per erythro- cyte, gm., $\times 10^{-11}$ Hb	Average iron per erythro- cyte, mg., $\times 10^{-11}$ Ic	Hb Ic
1	M	56	Cirrhosis of liver	11.7	75	4.2	35	37.0	0.90	0.98	1.0	83.3	0.97	3.08	314
2	F	48	Pericious anemia	11.7	75	3.4	35	37.0	1.11	0.98	1.0	102.9	1.20	3.80	315
3	M	58	Pericious anemia	14.0	90	4.2	42	44.5	1.08	0.98	1.0	100.0	1.40	4.45	315
4	M	28	Pulmonary tuberculosis	11.7	75	4.2	39	40.0	1.00	0.88	1.0	92.8	1.08	3.71	291
5	F	43	Carcinoma of stomach	12.6	81	4.5	38	40.3	0.91	0.98	1.0	84.4	1.06	3.40	311
6	F	39	Carcinoma of stomach	4.9	32	2.0	16	16.3	0.86	0.92	1.0	80.0	0.39	1.30	300
7	F	42	Carcinoma of cervix	5.9	38	2.6	20	21.1	0.83	0.87	1.0	76.9	0.45	1.62	277
8	M	21	Pneumonia	10.9	70	3.6	35	36.4	0.99	0.92	1.0	97.2	1.07	3.53	303
9	F	50	Chronic cardiovascular disease	10.1	65	3.3	30	32.4	0.98	0.99	1.0	90.9	0.91	2.94	309
10	M	45	Gastr. ulcer, possibly carcinoma	10.7	69	3.7	34	37.0	0.99	0.93	1.0	91.8	0.98	3.39	289
11	M	30	Pneumonia	7.8	50	2.8	24	26.0	0.93	0.95	1.0	85.7	0.67	2.22	301
12	F	55	Hodgkin's disease	6.3	41	2.4	24	26.0	0.95	0.78	1.0	100.0	0.63	2.60	242
13	M	15	Lymphatic leukemia	5.4	35	2.1	19	21.3	0.99	0.84	1.0	90.4	0.48	1.92	250
14	F	54	Carcinoma of liver	6.24	40	2.6	19	79.5	0.80	0.96	1.0	70.8	0.44	1.41	312
15	F	26	Acute bronchitis	11.7	75	4.1	37	38.3	0.97	0.98	1.0	90.2	1.05	3.45	304
16	F	67	Carcinoma of liver	9.67	62	3.6	33	35.1	0.98	0.86	1.0	91.3	0.89	3.20	278
17	F	61	Carcinoma of pancreas	9.51	61	3.4	31	32.5	0.99	0.90	1.0	91.1	0.86	2.96	294
18	M	53	Carcinoma of rectum	7.02	45	2.4	22	23.2	0.98	0.94	1.0	91.6	0.64	2.45	261
19	F	62	Chronic cholecystitis	10.1	65	3.3	30	30.3	0.97	0.99	1.0	90.9	0.91	2.75	330
20	F	23	Septic endometritis	7.8	50	3.0	23	23.3	0.97	0.95	1.0	76.6	0.59	1.78	331
21	F	43	Tertiary lues	10.9	70	3.6	32	34.0	0.96	1.00	1.0	88.8	0.96	3.01	315
22	M	23	Chancroid	11.7	75	3.9	35	36.7	0.97	0.98	1.0	89.7	1.04	3.27	315
23	F	39	Tuberc	10.9	70	3.7	32	33.5	0.94	0.99	1.0	86.4	0.91	2.89	332
24	M	46	Influenza	11.0	71	3.7	33	35.7	0.96	0.98	1.0	89.1	0.98	3.12	314

ANEMIAS (IRON VOLUME INDEX 1)—Continued.

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	R.R.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Satura- tion index.	Iron volume index.	Average vol. of erythro- cyte, cubic microns.	Average Hb. per erythro- cyte, gm. × 10 ⁻¹¹ Hbe	Average iron per erythro- cyte, mg. × 10 ⁻¹¹ Ic	Hbe Ic
25	F	74	Chronic nephritis	10.9	3.8	35	37.5	0.97	0.94	1.0	92.1	1.00	3.45	287
26	F	60	Lymphatic leukemia	10.9	3.6	32	34.0	0.99	1.00	1.0	88.8	0.96	3.01	318
27	F	61	Chronic myocarditis	11.8	4.0	36	38.3	0.98	0.97	1.0	90.0	1.06	3.44	306
28	F	50	Arteriosclerosis	10.1	3.4	31	33.0	0.99	0.96	1.0	91.1	0.92	3.00	306
29	F	51	Chronic myocarditis	9.2	3.7	27	33.0	0.92	1.00	1.0	84.3	0.77	1.76	438
30	F	42	Acute appendicitis	12.1	78	4.0	36	0.97	0.99	1.0	90.0	1.08	3.30	321
31	F	63	Chronic cholecystitis	11.8	76	4.0	36	0.97	0.97	1.0	90.0	1.06	3.42	349
32	F	50	Chronic myocarditis	10.1	65	3.0	32.4	0.90	0.99	1.0	83.3	0.84	2.69	312
33	F	25	Pulmonary tuberculosis	10.9	70	4.0	36	0.97	0.97	1.0	90.0	0.98	3.37	290
34	F	68	Arteriosclerosis	10.9	70	3.9	35	0.94	0.92	1.0	92.0	0.98	3.41	281
35	F	49	Chronic arthritis	11.3	73	3.8	36.3	0.97	0.98	1.0	89.4	1.01	2.90	341
36	F	70	Pernicious anemia	11.5	74	3.2	36	1.20	0.94	1.0	112.3	1.29	4.31	276
37	M	30	Exophthalmic goiter	9.9	64	3.3	30	0.98	0.98	1.0	90.9	0.89	2.92	304
38	M	60	Carcinoma of rectum	9.6	62	3.2	29	0.99	0.98	1.0	90.6	0.86	2.62	328
39	F	35	Chronic sinusitis	11.7	75	3.9	34	0.94	1.00	1.0	87.2	1.02	2.99	341
40	M	21	Diabetes	12.1	78	4.0	36	0.97	0.99	1.0	90.0	1.08	3.42	315
41	M	50	Duodenal ulcer	12.4	80	4.1	42	0.91	0.87	1.0	102.4	1.27	4.45	285
42	F	20	Carcinoma of stomach	11.7	75	4.0	36	0.97	0.95	1.0	90.0	1.05	3.43	306
43	F	62	Carcinoma of rectum	11.5	74	3.8	34	0.97	1.00	1.0	89.4	1.02	3.17	320
44	F	50	Carcinoma of gall bladder	10.9	70	3.7	34	0.99	0.91	1.0	91.9	1.00	3.16	316

ANEMIAS (IRON VOLUME INDEX LESS THAN 1).

Case.	Sex.	Age.	Diagnosis.	Hb., gm. per 100 cc.	R.R.C., millions per c.mm.	Cell vol., per 100 cc.	Iron, mg. per 100 cc.	Volume index.	Satura- tion index.	Iron volume index.	Average vol. of erythro- cyte, cubic microns.	Average Hb. per erythro- cyte, gm. × 10 ⁻¹¹ Hbe	Average iron per erythro- cyte, mg. × 10 ⁻¹¹ Ic	Hbe Ic
1	M	63	Gastric ulcer	12.4	4	37	34.0	0.98	0.89	0.91	90.2	1.11	3.06	362
2	M	60	Bronchiectasis	8.1	2.9	24	23.4	0.89	0.99	0.97	82.7	0.66	1.93	342
3	F	14	Perinephritic abscess	7.0	4.4	21	19.6	0.97	0.76	0.91	89.5	0.61	1.75	348
4	F	22	Miscariage, hemorrhage	6.8	3.0	27	25.6	0.97	0.75	0.94	90.0	0.61	2.30	265
5	F	20	Incompl. abortion, hemorrhage	10.1	65	32	29.0	0.89	0.93	0.90	82.0	0.82	3.31	243
6	F	22	Incompl. abortion, hemorrhage	10.1	65	27	18.0	0.88	0.94	0.81	81.4	0.56	1.46	282
7	F	45	Fistula of colon	11.2	72	34	32.0	0.97	0.97	0.94	89.3	0.90	2.85	317
8	F	27	Chr. endometritis, menorrhagia	11.7	73	3.0	25	0.90	0.92	0.88	83.3	0.64	1.83	350
9	F	55	Essential hypertension	7.8	3.0	25	22.0	0.90	0.95	0.95	83.3	0.97	2.68	362
10	F	20	Abortion, hemorrhage	11.7	75	4.2	35	0.97	0.96	0.89	90.0	1.06	2.88	357
11	F	31	Pulmonary tuberculosis	11.8	60	3.6	32.0	0.97	0.96	0.89	90.3	0.83	2.25	373
12	F	35	Carcin. of kidney, hematuria, nephrectomy	9.3	60	3.3	25.0	0.95	0.96	0.93	84.8	0.78	2.12	367

expresses the amount of hemoglobin per unit volume of cell in relation to normal. The color index gives us the amount of hemoglobin per cell in relation to normal but does not take into consideration the cell volume. The iron index of Murphy has a similar defect, expressing iron in relation to the number of red blood cells without considering their volume.

The present studies are intended to establish a new corpuscular iron index which considers whole blood iron as related to cell volume. It is calculated by dividing the iron as expressed by percentage of normal by the cell volume as expressed by percentage of normal. In each case the average volume of the erythrocyte and average hemoglobin and iron per erythrocyte were also calculated. There seems to be some relationship between the hemoglobin and the iron content of the blood, and this was expressed by dividing the hemoglobin per erythrocyte by the iron per erythrocyte. The volume index and the saturation index were tabulated in each instance to aid in correlating the iron content of the cells with their size and hemoglobin content. These studies were carried out on 100 hospital patients. About half were normals. By normals we mean hospital patients showing no anemia and therefore, presumably, no derangement in their iron metabolism. The other half are patients suffering from anemias of the usual types.

Technique. Twenty cubic centimeters of blood are withdrawn from the arm vein and 10 cc. are run into a 15-cc. graduated centrifuge tube containing 2 cc. of a 1.6 per cent sodium oxalate solution. This is mixed by inverting, and centrifuged at 2500 r. p. m. for 1 hour. The total cell volume per cent is then read off and calculated for 100 cc.

The other 10 cc. are shaken up in a test tube previously prepared by evaporating 2 cc. of 1.6 per cent iron-free sodium oxalate solution to dryness. The sodium oxalate used was obtained from the Bureau of Standards and shown by controls to contain no iron. This blood is used for hemoglobin, red blood cell and iron determinations. The hemoglobin was done by both the Sahli and Newcomer methods in each case, and 15.6 gm. of hemoglobin were taken as 100 per cent. Red blood cell counts were done with two standardized pipettes, a drop from each being counted for every determination, and the two averaged. Results were not accepted if the error was more than 2 per cent.

Although several methods have been proposed for the determination of iron in the blood, no one method was found that would meet all the conditions necessary for accuracy and convenience. The simplest method for digestion of the blood uses the sulphuric acid-potassium perchlorate mixture proposed by Wong.⁶ However, this author uses an aqueous solution of ferric sulphocyanate for the colorimetric quantitative procedure. The color is due to nonionizable ferric sulphocyanate, the aqueous solutions of which hydrolyze very rapidly, thus making this method inaccurate.

Further improvements in iron determinations consisted in the extraction of this color with amyl alcohol, ether, or a combination of both, and the procedure of Stokes and Cain⁷ employing these mediums was found to be the most accurate and satisfactory. By this method the colors obtained are pure and do not fade. The possibility of the reduction of the ferric ion is eliminated by the use of persulphate. The oxidation of the sulphocyanic acid to isopersulphocyanic acid, which is yellow and interferes seriously

with the matching of the colors, is prevented by the use of the double salt of mercuric sulphocyanate sulphocyanic acid. The only objectionable feature of this method is the amyl alcohol, which is very irritating to the mucous membranes of the nose and throat of the investigator. The amyl alcohol may be replaced by the extraction mixture proposed by Bernhard and Drekter,⁸ which was found to be just as efficient, nonirritating, and the colors are more easily matched.

Reagents. *Standard Iron Solution.* *Standard A:* Dissolve 0.702 gm. ferrous ammonium sulphate in about 50 cc. of water. Add 20 cc. of 10 per cent iron-free sulphuric acid. Warm and then add $\frac{N}{10}$ potassium permanganate until a faint pink color persists. Dilute to 1 liter; 1 cc. will contain 0.1 mg. of iron. *Standard B:* Standard A diluted with an equal volume of water; 1 cc. will contain 0.05 mg. of iron.

Sulphocyanic Acid. One hundred grams of ammonium thiocyanate are dissolved in 100 cc. of 65 per cent by weight sulphuric acid. Measure volume, transfer to separatory funnel and shake out immediately with three-fourths volume of amyl alcohol. Discard the aqueous solution and again shake out twice with an equal volume of water. Combine the water extracts, which together contain about 7 per cent of sulphocyanic acid. Saturate with mercuric sulphocyanate so that some remains on the bottom. Allow to stand over night in a dark bottle.

Persulphate Solution. A saturate solution of C. P. iron-free sodium persulphate in distilled water.

Extraction Mixtures. (1) Five parts of amyl alcohol and 2 parts of ether; (2) equal parts of ethylene glycol monobutyl ether and ethyl ether.

FORMULA FOR FIGURING THE IRON.

$$S \times \frac{R_s}{R_x} \times 500 = \text{mg. of iron.}$$

S = strength of standard.

R_s = reading of standard.

R_x = reading of unknown.

CALCULATIONS:

				Normal values.
	$\frac{Cv}{46}$	Total cell volume, per cent	$\frac{46}{46}$	
Volume index	$= \frac{RV}{5.0}$	Normal cell volume, per cent	$\frac{46}{5}$	$= 1$
		R. B. C. in millions	$\frac{5}{5}$	
		Normal R. B. C. in millions	$\frac{5}{5}$	

$$\text{Saturation index} = \frac{\frac{Hb\%}{100}}{\frac{Cv}{46}} = \frac{\frac{100}{100}}{\frac{46}{46}} = 1$$

$$\text{Corpuscular iron index} = \frac{\frac{I}{45}}{\frac{Cv}{46}} = \frac{\text{Iron in mg. per 100 cc.}}{\text{Average iron in mg. per 100 cc.}} = \frac{45}{46} = 1$$

$$\text{Average volume of erythrocyte (Ev)} = \frac{Cv \times 10^{12}}{R_{100} \times 10^{11}} \text{ cubic micron} = \frac{46^{12}}{5^{11}} = 92$$

$$\text{Average Hb per erythrocyte (Hbe)*} = Hb (\text{gm.}) \times Ev \times 10^{-10} = (15.6 \times 92) = 1.43$$

$$\text{Average iron per erythrocyte (Ie)*} = I \times Ev \times 10^{-10} = (45 \times 92) = 4.4$$

* In the tables these determinations, namely, average Hb and average iron, are expressed as $\times 10^{-10}$ by pointing off three more places.

The ether does not have to be of special purity, as the presence of mercuric sulphocyanate prevents the oxidation of the sulphocyanic acid by the peroxids in the ether.

IRON DETERMINATIONS. One cubic centimeter of blood is diluted with 4 cc. of water and 1 cc. of the mixture is digested according to the method of Wong. After being allowed to cool it is diluted to approximately 10 cc. and a drop of persulphate is added, followed by exactly 25 cc. of the extraction medium and 5 cc. of the sulphocyanic acid reagent. The tube is then tightly fitted with a rubber stopper, the mixture is well shaken and after a few minutes' standing separates into two distinct layers. If this separation does not take place rapidly it can generally be accelerated by the addition of a few cubic centimeters of water. One cubic centimeter each of Standards A and B are then digested and treated in the same manner. The A Standard is suitable for figures within the normal range (35 to 50) and the B Standard is used where the iron values are lower than the normal. Since the A Standard contains 0.1 mg. of iron and the B Standard 0.05 mg. of iron, and 0.2 cc. of blood are used, the formula for figuring the iron is as found on p. 642.

Discussion. Analysis of the data shows that the majority of the normal cases have an iron volume index of 1. In a small number it is between 0.9 and 1, so that 0.9 can be taken as the lower limit of normal. When the iron volume index is 1 it means that the red blood cells are saturated with iron and it is to be expected that there will be no response to iron therapy. Strange as it may seem, the majority of the anemias also have an iron volume index of 1, and this would mean that in these cases of anemia, iron is also of no value. This is easily understood in the cases of pernicious anemia, leukemia and Hodgkin's disease. There are, however, a large number of patients with secondary anemia in this group and these require more detailed explanation. The latter are noticeably mostly patients with carcinoma or those suffering from acute or chronic infections with fever. In their report on the treatment of secondary anemia with iron, Smithburn, Masters and Zerfas⁹ state that patients suffering from the diseases just mentioned do not respond readily to iron therapy. They give as a reason that fever, infection or intoxication may be responsible for temporary or complete inhibition of the hematopoietic response to iron. In our series such cases show an iron volume index of 1. This seems to indicate that the lack of response to iron treatment is due to the fact that the cells are already saturated with iron rather than that toxic influences are depressing the bone marrow. Those cases of anemia in which the iron volume index is under 0.9 are notably patients who have suffered from direct loss of blood or from some nutritional disorder. It is interesting to note here that two of the normals also had an iron volume index of less than 0.9 despite a normal hemoglobin and red blood cell count. According to our theory the red blood cells are not completely saturated with iron when the iron volume index is below 0.9, and iron should be of therapeutic value in these cases. This experimental observation is

borne out clinically, as we know that patients with secondary anemia following hemorrhage respond most readily to iron treatment.

The iron volume index determination seems to be of value, therefore, in determining which case of anemia will respond to iron. If the red cells are already saturated with iron, as shown by a normal index, further iron therapy is useless.

The determinations of hemoglobin and iron per red cell, while largely of academic interest, indicate quite plainly the well known lack of parallelism between the quantities of hemoglobin and iron in the blood. Iron has a definite place in the hemoglobin molecule, and the relationship of molecular hemoglobin and molecular iron is about 300.¹⁰ Our ratio $\frac{\text{Hb.}}{\text{I}}$ is subject to considerable error, but in some cases there are wide variations above and below that figure which cannot be considered within the limit of error. When the ratio is much lower than 300 it means that there is more iron than can combine with the hemoglobin. This excess iron may be in a prehemoglobin state or in the form of some decomposition product of hemoglobin. When the ratio is much higher than 300 there appears to be more hemoglobin than iron. This might indicate that the hemoglobin is in molecular combination with other substances besides iron, or that other substances besides hemoglobin give its color reaction.

Further investigations on these subjects are planned.

Conclusions. 1. A new corpuscular iron index has been devised in an attempt to correlate the iron in whole blood with cell volume.

2. The normal figure for this index is between 0.9 and 1.0 and when this index is 1.0 the red cells are regarded as saturated with iron.

3. An iron volume index of 1.0 is obtained in most normal people and in cases of pernicious anemia, leukemia and in secondary anemias associated with carcinoma and acute and chronic infections with fever. Iron therapy seems to be of no value in these cases, due to the fact that the red cells are already saturated with iron.

4. An iron volume index of less than normal is most commonly found in cases of secondary anemia caused by malnutrition or loss of blood. Iron is of decided therapeutic value in the treatment of these patients.

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BIBLIOGRAPHY.

1. Menghini: Quoted in *Arch. de m'd. d. enfants*, 1930, 33, 668.
2. Murphy, W. P., Lynch, R., and Howard, I. M.: The Value of Determinations of the Iron Content of Whole Blood, *Arch. Int. Med.*, 1931, 47, 883.
3. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, *Am. J. Med. Sci.*, 1931, 181, 597.

4. Wintrobe, M. M.: Volume and Hemoglobin Content of Red Blood Corpuscle. Simple Method of Calculation, Normal Findings and Value of Such Calculations in Anemias, *Am. J. Med. Sci.*, 1929, 177, 513.

5. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards. Redeterminations Based on Findings in 137 Healthy Young Men, *Arch. Int. Med.*, 1926, 37, 685.

6. Wong, S. Y.: *J. Biol. Chem.*, 1923, 55, 422.

7. Stokes, H. N., and Cain, J. R.: *Yoe's Photometric Chemical Analysis*, John Wiley & Son, 1928, 1, 218.

8. Bernhard, A., and Dreker, I. J.: To be published.

9. Smithburn, K. C., Masters, J. M., and Zervas, L. G.: The Treatment of Secondary Anemia, *J. Lab. and Clin. Med.*, 1931, 16, 858.

10. McLeod, J. J. R.: *Physiology and Biochemistry in Modern Medicine*, St. Louis, C. V. Mosby Company, 1920, p. 92.

THE CLINICAL VALUE OF THE UNCORRECTED COLOR INDEX AND OF CELL SIZE IN PERNICIOUS ANEMIA.

BY S. MILTON GOLDHAMER, M.D.,

INSTRUCTOR IN MEDICINE.

WITH THE TECHNICAL ASSISTANCE OF A. FRITZELL, B.S., E. DAVIDSON, M.S.,
AND C. STEEN, B.S.,

ANN ARBOR, MICH.

(From the Thomas Henry Simpson Memorial Institute for Medical Research,
University of Michigan.)

CONFUSION concerning the hemoglobin content of the red blood cells,¹ and the inaccuracy of many hemoglobin estimations as compared with van Slyke's method,² cast doubt on the value of the uncorrected color index in the diagnosis of pernicious anemia. Many observers, as Herz, Capps, Wroth, Larabee and Rosedale, stress the preferability of the "volume index," as based on more accurate laboratory methods, while Haden,¹ in 1925, pointed out the value of the "saturation index." Osgood³ used the "hemoglobin coefficient" and "volume coefficient" as simplifying Haden's calculations, while Wintrobe⁴ offered the "absolute cell determinations" as substitutes.

The commonness of color index estimation, without any correction, its ease and facility, and the interpretation given results, make it important diagnostically to establish the true value of the routine color index.

The color index $\left(\frac{\% \text{ of hemoglobin}}{\% \text{ of red blood cells}} \right)$ is based on the assumption that a normal person has 100 per cent hemoglobin and a red blood cell count of 5,000,000 cells as equivalent to 100 per cent. These figures do not take into consideration such variable factors

as sex, age, size, altitude, time of day, the different "normal" values of hemoglobin, and the like; thus representing an "uncorrected" rather than a "corrected" color index.

The figures for average normal red blood cell counts (5,000,000 per c.mm. for men and 4,500,000 for women) were adopted a long time ago, and continued without proper confirmation. Vierordt (1852) and Welcker (1854), each of whom examined the blood of only 2 persons are responsible for these figures. Recently Osgood,³ Rud, Wintrobe and Miller, Horneffer, Komicki and Haden have published more accurate data on normal averages in various localities, finding a wide range of variations, with averages ranging from 4,870,000 to 5,600,000 red cells per cu. mm. Because of the unavoidable error in the method of counting the red blood cells, which may amount to $250,000 \pm$, 5,000,000 is arbitrarily assumed as normal in calculating the results obtained.

The literature on normal hemoglobin standards is of but slight value because so many different methods of hemoglobin estimations have been used. Most observers have employed hemoglobinometers graduated to read in per cent with no agreement as to what shall be the equivalent to 100 per cent. In compiling the data to be discussed later, the Sahli hemoglobinometer (Leitz), in which 14 gm. of hemoglobin are equivalent to 100 per cent, was used, calibrated and checked with the van Slyke² gas method.

A third factor to be considered as related to the color index is the measurement of red blood cell diameters. Although it does not enter into the calculation of the color index, it is probably an important factor in explaining increasing or decreasing values of the color index in the various anemias.⁵

Data. One hundred treated cases of pernicious anemia, chosen at random, were divided into male and female series and such necessary calculations were made to give weekly averages of the results so that the individual error could be minimized. These cases were followed with daily blood counts for periods ranging from 2 to 4 weeks and then at frequent intervals for more than 1 year. There were 679 observations made. The red blood cell counts were made on a Neubauer-Levy counting chamber (new ruling, U. S. Bureau of Standards). The hemoglobin was calculated in a Sahli hemoglobinometer in the usual manner with $\frac{N}{10}$ hydrochloric acid, allowed to stand for 1 minute, diluted with distilled water, and compared with a colored glass rod standard. Cell measurements were made on all cases at the time of admission to the hospital and on many at the time of discharge. These measurements were made on Wright-stained cover slip preparations, with an eyepiece micrometer. (According to some observers this procedure is recognized as giving smaller diameters than the "wet" methods). The resulting figures were plotted on ruled paper for comparison with the normal Price-Jones curve.

TABLE 1.—AVERAGE COLOR INDEX IN 100 CASES OF PERNICIOUS ANEMIA ON ADMISSION AND A YEAR OR MORE AFTER EFFECTIVE TREATMENT.

Total cases, 100.	Total observations, 679.	Admission.		First week.		Second week.		Third week.		Fourth week.		Two months.		Three months.		Four months.		Five months.		Six months.		One year or more.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Male 64	Observations	124	67	60	33	56	31	40	19	43	19	43	20	22	15	12	7	15	7	13	6	18	9
	Highest color index	1.70	1.50	1.60	1.70	1.50	1.30	1.50	1.40	1.40	1.08	1.40	1.40	1.20	1.08	1.02	1.20	1.20	1.10	1.10	0.98	1.50	1.04
	Lowest color index	0.70	0.77	0.79	0.90	0.76	0.86	0.70	0.88	0.69	0.70	0.62	0.70	0.64	0.55	0.71	0.65	0.73	0.83	0.78	0.85	0.80	0.63
Female 36	Average color index	1.17	1.12	1.16	1.10	1.10	1.06	1.10	1.06	1.05	1.02	0.92	0.92	0.88	0.81	0.91	0.91	0.94	0.93	0.94	0.91	1.00	0.90

In analyzing the figures (Table 1 and Fig. 1) several important features present themselves. The average color index of the female series is always less than that of the male series, due probably to constitutional variations. It is also to be noted that the uncorrected color index falls below 1 at some time between 4 and 8 weeks after the onset of treatment, although individual readings may be above or below 1 at any time during complete relapse up to 1 year or more with treatment. Although the figures for each type of treatment have not been listed separately, it was observed that the color index was influenced in a like manner by liver, liver extract and ventriculin.

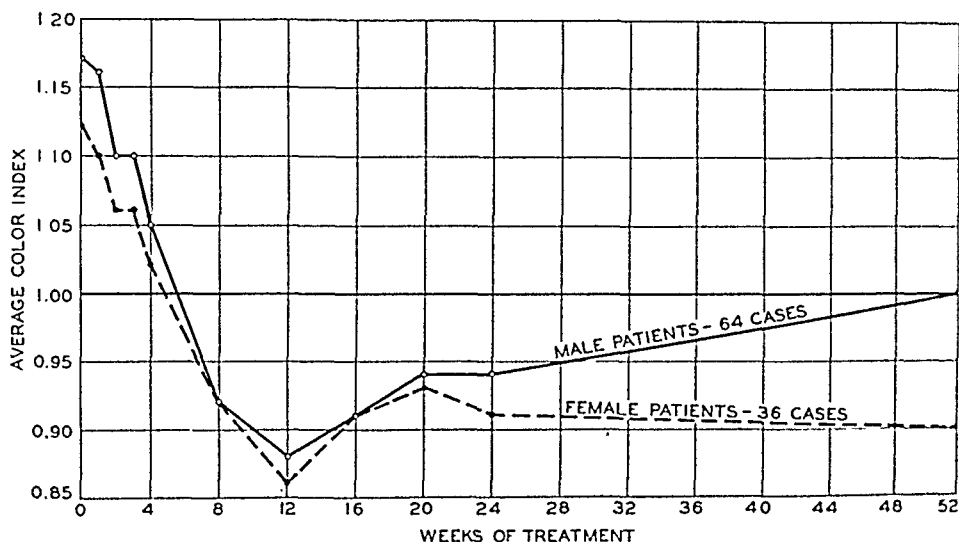


FIG. 1.—Effect on average color index with various types of adequate therapy in pernicious anemia. Five million R. B. C. per c.mm. and 14 gm. Hb. per 100 cc. regarded as 100 per cent.

In a comparison of the color index and the red blood cell count (Table 2) it was observed that the same variations exist in the individual values of the index, some readings being below 1, others above 1, regardless of the red blood cell count; however, the lower the red blood cell count, the higher was the color index average. As the arbitrary standard of normal for the red blood cells was approached, following treatment, the color index tended to approximate unity. Between the range of 4,000,000 and 5,000,000 red cells per c.mm. a level was reached at which the color index becomes 1 or less.

In 15 of the foregoing cases cell measurements were made on entrance (before treatment) and at discharge. The percentage of cells larger than 7.5 micra was estimated in each case and these results were plotted against the number of millions of red blood

cells. The results obtained substantiate the findings of Medearis and Minot.⁶ As the blood picture approaches normal in treated cases, the percentage of extremely large cells diminishes in amount and returns to within the normal range (Fig. 2).

TABLE 2.—COLOR INDEX AS COMPARED WITH MILLIONS OF RED BLOOD CELLS FOLLOWING TREATMENT.

	Red blood cells in millions per c.mm.				
	0 to 1.	1 to 2.	2 to 3.	3 to 4.	4 to 5+.
Admission	1.15	1.12	1.15	1.01	0.93
1 week	1.26	1.16	1.10	1.03	0.89
2 weeks	1.07	1.07	1.09	0.95
3 weeks	1.10	1.21	1.07	1.04	0.93
4 weeks	1.23	1.08	1.03	0.88
8 weeks	1.04	0.97	0.87
12 weeks	1.01	0.86
16 weeks	0.97	0.89
20 weeks	1.06	0.91
24 weeks	0.92	0.93
52 weeks	1.10	0.91

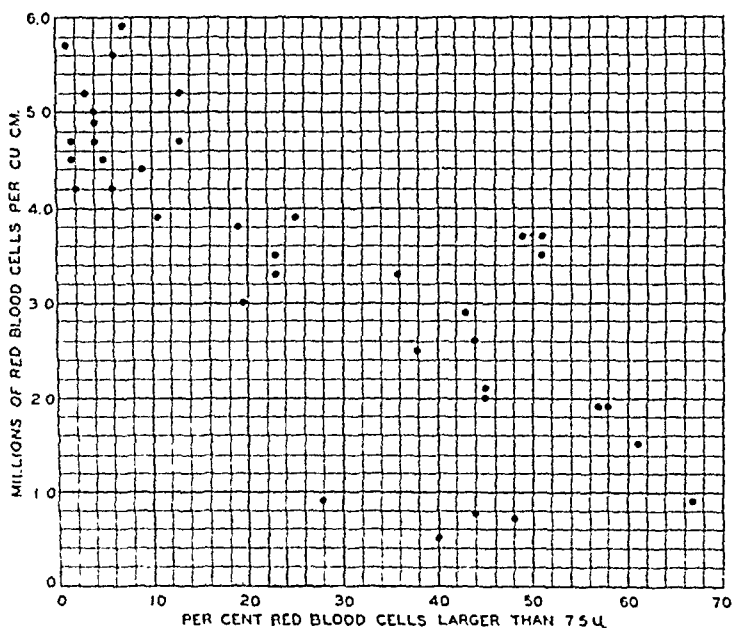


FIG. 2.—The relationship of the percentage of large red blood cells and red blood cell count in treated cases of pernicious anemia.

When the percentage of cells larger than 7.5 micra in untreated cases is plotted against the red blood cell count at the time of entrance (Fig. 3) there appears to be no simple relationship. It is interesting to note, however, that regardless of whether a patient is just beginning to relapse or has a severe anemia, the large cells are very much in evidence. This is probably one of the very earliest changes in the blood. Since, in cases sufficiently treated, the percentage of large cells varies directly with the degree of the

anemia,⁶ being within the range of normal when a mild anemia is present; and since in untreated cases the percentage of large cells is increased, regardless of the severity of the anemia, this factor may be used as a differential point to note whether a patient is beginning to relapse or not.

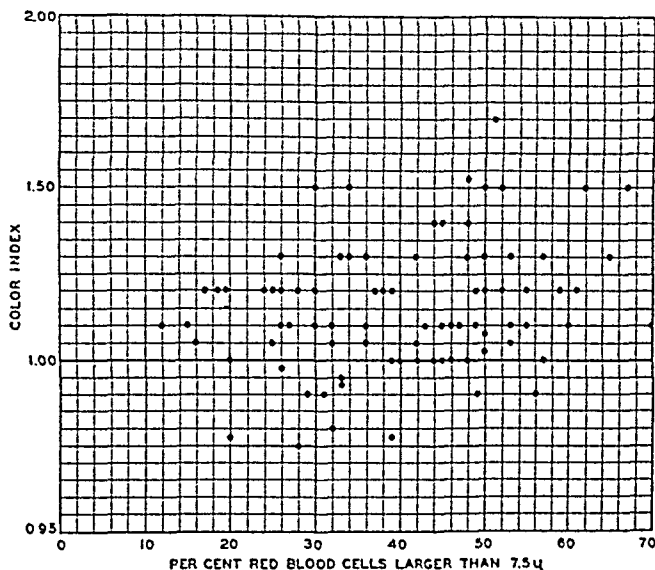


FIG. 3.—The relationship between the percentage of large red blood cells and color index in untreated cases of pernicious anemia.

Case Abstracts. CASE 1.—Mr. W. W. (No. 233360) was admitted on January 23, 1930, with a red cell count of 1,800,000 per c.mm. and hemoglobin 44 per cent (Sahli). The Price-Jones curve showed a secondary peak at 9 micra, with 28.5 per cent of the cells larger than 7.5 micra. After 2 months' treatment with ventriculin the red blood cells were 4,300,000 per c.mm. and hemoglobin 85 per cent (Sahli). On a maintenance dose of 50 gm. of ventriculin per week the blood remained within normal limits for about 1 year. In December, 1930, he discontinued his full dosage and by January 12, 1931, the red blood cells had fallen to 3,100,000 per c.mm., with a hemoglobin of 80 per cent (Sahli). Measurement of the cells at this time showed 30 per cent larger than 7.5 micra. After careful questioning of the patient no symptoms of relapse were elicited. With the laboratory findings a definite diagnosis of pernicious anemia in early relapse could be made.

This case illustrates the presence of large cells in greatly increased numbers early in relapse. Their presence becomes a valuable diagnostic point when one considers a patient with a count of 4,000,000 red cells per c.mm., with adequate treatment, and a similar count in a patient with inadequate treatment. In the former case the percentage of cells larger than 7.5 micra will be less than 5 per cent, whereas in the latter the percentage will range from 20 to 30 per cent. This factor will serve as a valuable differential

feature, in the diagnosis of pernicious anemia when the red blood cell count is around 4,000,000 per c.mm., and is present even in the absence of an increased bilirubinemia and when the degree of poikilocytosis is too small to aid in the diagnosis.

In Fig. 4 the percentage of cells larger than 7.5 micra is plotted against the color index in untreated cases. From this, it can be seen that there is no definite correlation between the two. Nevertheless, it is noted that with a high color index the percentage of cells larger than 7.5 micra is greatly increased.

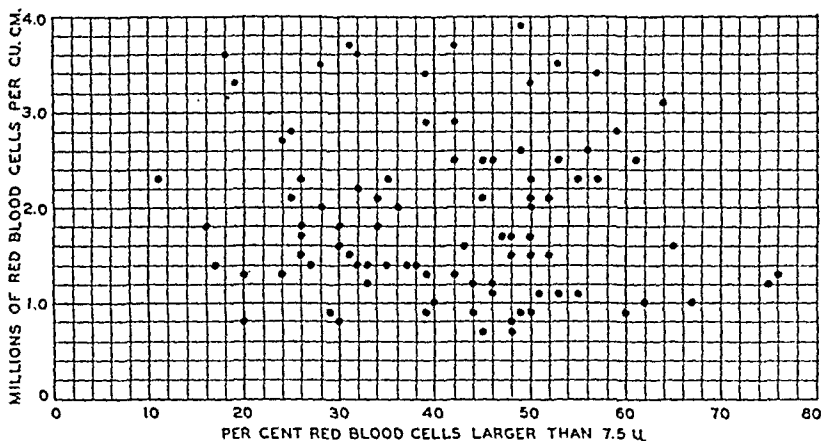


FIG. 4.—The relationship of the percentage of large red blood cells and red blood cell count in untreated cases of pernicious anemia.

Discussion. Of the various criteria used in the differential diagnosis of pernicious anemia, the three outstanding tests have been the absence of free hydrochloric acid in the gastric secretion, the high color index and the macrocytosis. Within the past few years there have been published a few series of cases demonstrating that practically all patients with pernicious anemia have no free hydrochloric acid in their gastric contents; occasionally an isolated case has been reported contradictory to these findings. However, none of these cases have ever been definitely proven as being true pernicious anemia at autopsy. Sturgis⁷ states that at one time it was generally accepted that gastric anacidity and a high color index were the two most constant features in pernicious anemia. According to Haden,⁵ "A color index greater than 1, when correctly determined, is usually regarded as the most constant and characteristic blood finding in pernicious anemia." Recently there have been observed a few cases of pernicious anemia complicated by hemorrhage, tumors, chronic infections, glandular dystrophies, or a food deficiency, which gave a color index of a secondary anemia rather than a primary anemia. These cases had most of the characteristics of pernicious anemia and responded in the usual manner to the treatment for this disease.

CASE 2.—Mrs. A. B. (No. 2066267) had pernicious anemia and a pelvic tumor. The Price-Jones curve of red blood cell measurement showed a secondary peak at 8.2 micra, with 14 per cent of the cells larger than 7.5 micra. There was also another peak at 6.3 micra, which was suggestive of a secondary anemia. Her reticulocyte rise reached a maximum of 35 per cent in 7 days, but at no time was her color index more than 1. It varied as follows: On admission, 0.83; 1 week after treatment, 0.81; 2 weeks after treatment, 0.75; 1 year after treatment, 0.63.

CASE 3.—Mr. P. (No. 215315) had pernicious anemia complicated by chronic nephritis. His Price-Jones curve showed 23.5 per cent cells larger than 7.5 micra and 64 per cent smaller. With liver extract he had a characteristic rise of reticulocytes, reaching a maximum of 27.5 per cent. On entrance his red cell count was 1,480,000 per c.mm., with a hemoglobin of 15 per cent (Sahli). The color index was 0.5. Weekly blood studies showed a color index less than 1 on all occasions for a period of 2 months. At the time the patient died, of chronic nephritis, his red cell count had increased to 3,900,000 per c.mm. and the hemoglobin to 54 per cent (Sahli).

Other cases have been collected in which the color index was low due to the fact that the primary disease was complicated by some infection, tumor, hemorrhage or food deficiency. Sufficient evidence is thus obtained to prove that in individual cases of pernicious anemia the color index may be less than 1 at all times. In the whole series of cases collected, several individual counts have been recorded giving a color index less than 1. The color index becomes of value, then, only as a substantiating factor when other signs and symptoms of pernicious anemia are present. Further, if the color index is always less than 1 and the diagnosis of pernicious anemia is definitely established, there must be present some complicating factor.

It is possible now to answer the original question as to the clinical value of the uncorrected color index in the diagnosis of pernicious anemia. One reading in itself is of little value, for the reading may or may not be above 1. However, over a period of time, with several readings, its importance is well appreciated. Individual readings above 1 are not pathognomonic of pernicious anemia, but serial readings may be used as substantiating evidence.

Regardless of the indices used or the "absolute cell determinations," a standard must be employed. Since it is physically impossible to establish a normal on account of such factors as time, age, sex, race, climate, season, digestion, dehydration, water administration, diet, pregnancy and lactation, menstruation, vasomotor and psychomotor influences,⁸ all results have significance. One method or another may be more accurate as a laboratory procedure, but this is usually accomplished at the sacrifice of simplicity.

The normal standards for the various chemical constituents of the blood, such as sugar, bilirubin, chlorids, calcium, phosphorus and the like, are not "single figures," but comparatively wide ranges. The possibility of a single figure for any of these normals was ruled out when contributory factors were considered. For

similar reasons it would be better to consider the normal hemoglobin content of the blood as from 14 to 16 gm. per 100 cc.

The question might arise as to the difference in the results if 16 gm. of hemoglobin per 100 cc. of blood were used instead of 14 gm. as a standard for the calculation of the color index. The following table shows the difference in per cent reading of the two standards:

14 grams.	16 grams.
100	88
75	66
50	44
25	22

There exists a constant factor as a difference between the two so-called "normals" and although the higher of the two would reduce the numerical values of the color index somewhat, the general results would remain the same. The curves plotted from the results given in this paper would have almost a duplicate form at slightly lower numerical values. Further, the lower the percentage of hemoglobin, or the more severe the anemia, the closer the two values approximate each other, and, since the error in the method of estimation is about 3 to 5 per cent, the difference would become negligible.

Macrocytosis, although a constant feature in the blood picture of pernicious anemia in relapse, may occur in other anemias, as those produced by cancer metastasis to the bone marrow, sprue, fish tapeworm and certain lesions of the liver and pancreas. Cell size alone cannot be used as pathognomonic evidence in any anemia, hence its value is limited. However, the absence of macrocytosis in a patient with anemia makes the diagnosis of pernicious anemia highly improbable.

Conclusions. 1. The uncorrected color index represents the actual hemoglobin per cent reading (100 per cent as normal), over the percentage of red blood cells (5,000,000 being equivalent to 100 per cent), disregarding such factors as sex and the various hemoglobin standards.

2. Because of the wide range of normal red blood cell counts, 5,000,000 cells per c.mm. may be used as an average arbitrary standard. From 14 to 16 gm. of hemoglobin per 100 cc. of blood are suggested as a standard of normal.

3. The average and serial color indexes in uncomplicated cases of pernicious anemia are above 1 before treatment; those of the male series are higher than those of the female.

4. Regardless of type of effective treatment, the influence on the color index is the same; the average and serial color indexes remain above 1 for about 6 weeks after treatment is started, then become less than 1.

5. In untreated and uncomplicated cases the lower the initial red blood cell count the higher the average color index. As the red cell count approaches the arbitrary normal following adequate treatment, the color index tends to approximate unity. Within the range of 4,000,000 to 5,000,000 red blood cells per c.mm. a level is reached at which the color index becomes 1 or less.

6. A single color index determination is not always diagnostic in cases of pernicious anemia, as individual readings may be above or below 1; but during relapse the average color index is always above 1 unless some complication is present.

7. The color index may be influenced by such complications as hemorrhage, chronic infections, glandular dystrophies and food deficiencies.

8. The increase in the percentage of red blood cells larger than 7.5 micra in early relapse, regardless of the severity of the anemia, may be used as a factor differentiating pernicious anemia from secondary anemia.

9. In untreated cases of pernicious anemia a high color index is always associated with a marked increase in the percentage of cells larger than 7.5 micra.

10. The presence of increased numbers of large cells in a blood film, regardless of the red blood cell count, is one of the earliest and most constant findings of the blood in beginning relapse in pernicious anemia.

BIBLIOGRAPHY

1. Haden, R. L.: The Volume and Hemoglobin Content of the Erythrocytes in Health and Disease, *Folia hæmatol.*, 1925, 31, 113.

2. Van Slyke, D. D., and Neill, J. M.: Determinations of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.*, 1924, 61, 523.

3. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards: Redeterminations Based on Findings in 139 Healthy Young Men, *Arch. Int. Med.*, 1926, 37, 685.

4. Wintrobe, M. M.: Volume and Hemoglobin Content of Red Corpuscle: Simple Method of Calculation, Normal Findings and Value of Such Calculations in Anemias, *Am. J. Med. Sci.*, 1929, 177, 513.

5. Haden, R. L.: Value of Volume Index in Diagnosis of Pernicious Anemia, *J. Am. Med. Assn.*, 1924, 73, 671.

6. Price-Jones, C.: Diameters of Red Cells in Pernicious Anemia and in Anemia Following Hemorrhage, *J. Path. and Bact.*, 1922, 25, 487; Red Cell Diameters in 100 Healthy Persons and in Pernicious Anemia: Effect of Liver Treatment, *J. Path. and Bact.*, 1929, 32, 479; The Variation in the Sizes of Red Blood Cells, *Brit. Med. J.*, 1910, 2, 1418. Medearis, D. M., and Minot, G. R.: Studies on Red Blood Cell's Diameter: In Pernicious Anemia, Before and During Marked Remission, and in Myelogenous Leukemia, *J. Clin. Invest.*, 1927, 3, 541. Bell, J. R., Thomas, F. K., and Means, J. H.: Studies on Red Cell Diameter: In Health and in Pernicious Anemia, *J. Clin. Invest.*, 1926, 3, 229. Persons, E. L.: Studies on Red Blood Cell Diameter: Relative Diameter of Immature (Reticulocytes) and Adult Red Blood Cells in Health and Anemia, Especially in Pernicious Anemia, *J. Clin. Invest.*, 1929, 7, 615. Grosh, L. C., and Stifel, T. L.: Diameter of Red Blood Cells in Differentiation of Anemias, *Arch. Int. Med.*, 1925, 36, 874.

7. Sturgis, C. C.: Personal Communication.

8. Wintrobe, M. M.: The Erythrocyte in Man, *Medicine*, 1930, 9, 195.

STUDIES OF ANEMIA IN PREGNANCY.

I. GASTRIC SECRETION IN PREGNANCY AND THE PUERPERIUM.

BY MAURICE B. STRAUSS, M.D.,

AND

WILLIAM B. CASTLE, M.D.,

BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital; the Departments of Medicine and Tropical Medicine, Harvard Medical School.)

RECENT studies have again emphasized the significance of disturbances of the gastro-intestinal tract in the pathogenesis of remote and systemic conditions.^{1,2} The pathogenesis of certain cases of deficiency disease has been found by many workers to lie in part in disordered intestinal conditions. The work of Castle and his associates³ has indicated that the absence from the gastric secretions of a ferment-like substance is the main etiologic factor in the development of Addisonian pernicious anemia. Recently Keefer, Yang and Huang⁴ have observed the influence of prolonged diarrhea in the production of disturbances of nutrition and blood formation, and Eusterman and O'Leary⁵ have noted the effects of gastro-intestinal lesions in the etiology of certain cases of pellagra. The work of Mettier and Minot⁶ suggests that the hydrogen-ion activity of the upper intestinal tract may be of great importance in the absorption or utilization of materials necessary for blood formation.

These observations suggested to us that the study of the gastric secretions during the normal physiologic process of pregnancy might be of aid in determining the etiologic factors involved in the common anemias of pregnancy. Study of the gastric secretions rather than of other measures of gastro-intestinal function was made because of the relative ease of securing repeated observations on the same individuals and because of the apparent importance of these secretions in the pathogenesis of certain disturbances of blood formation not associated with pregnancy.

In this report only data on the gastric secretions will be presented; studies correlating hematopoiesis in the same individuals will be the subject of a separate communication.

Literature. The few studies of gastric secretion during pregnancy that have been made are uniform in indicating a high incidence of diminished and absent free HCl. In none of these studies has histamin been employed when the usual test meal failed to stimulate the secretion of free HCl. Nakai,⁷ in 1925, reported the results of single gastric analyses on each of 14 pregnant women, in which he

found an average free acidity of 22 cc. N/10 acid per 100 cc. during the first half of pregnancy and 27 cc. during the last half, as compared to an average of 31 cc. found by other Japanese investigators in nonpregnant women. Arzt,⁸ employing a test meal of shredded wheat and water, during the first trimester of pregnancy, found gastric anacidity in 5 patients, and an average of 11 cc. in 13 others. In 6 patients observed during the last half of pregnancy he found an average free acidity of 15 cc. In a subsequent study⁹ he found 29 of 50 patients lacking free HCl during the first trimester of pregnancy, 6 of whom reexamined in the last trimester of pregnancy averaged 11 cc. Recently Mason¹⁰ reported 4 patients with gastric anacidity and 2 with an average of 8 cc. during the first trimester of pregnancy.

Methods of Investigation. Following preliminary observations of secretory changes during pregnancy, 24 apparently normal women who reported for routine prenatal care were selected for study. They ranged in age from 20 to 36 years (average, 27.6 years). Five were primiparae; 1 was pregnant for the fourteenth time; the average number of pregnancies was 4 per patient. Gastric analyses were performed at approximately monthly intervals during gestation and again 7 to 10 days after delivery. A gastroduodenal catheter with an external diameter of 4 mm. was uniformly employed, as producing less gagging than tubes with metal bulbs. All patients had abstained from food for 12 hours before examination. The tube, lubricated with mineral oil, was passed to the fundus of the stomach, the fasting contents removed, 50 cc. of 7 per cent ethyl alcohol instilled and extraction undertaken 20 and 40 minutes later. If no free HCl could be detected by Töpfer's reagent in any of the 3 specimens, 0.3 mg.* of histamin hydrochlorid was then injected subcutaneously and extractions of gastric secretion made 20 and 40 minutes later.

Alcohol was used routinely because of its freedom from the buffer action of the older type of test meals. It has been noted that the acidity of specimens following the alcohol test meal is generally the same as or higher than those of bread or biscuit and water meals. As histamin, even in these small doses, is a more powerful stimulant than alcohol, its employment was limited to such patients as failed to secrete HCl after the alcohol test meal. In the histamin tests free HCl was either completely absent or present in subnormal amounts.

In all, 142 gastric analyses were performed on the 24 patients. The quantity, character, hydrogen-ion activity, free HCl and total acidity of all specimens were determined. The pepsin content of the highest acid secretion was estimated by the method of Mett.¹² (The gastric juice was diluted with an equal quantity of water and titrated to pH 1.4.) Free and total acidity were titrated with Töpfer's solution and phenolphthalein, respectively. Hydrogen-ion activity was determined colorimetrically with Clark and Lub's indicators.¹³

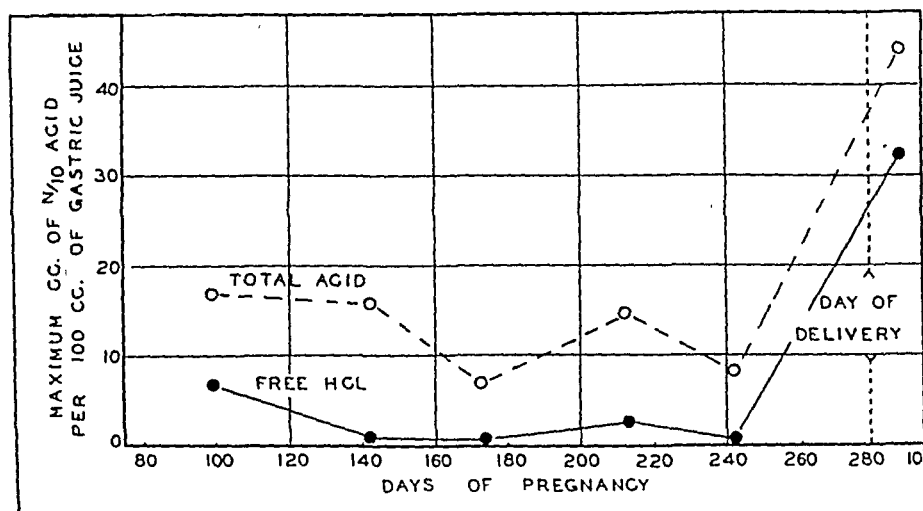
Results. In 18 gastric analyses performed by the same technique on nonpregnant women the maximum free-acid concentration varied from 19 to 76 cc. N/10 acid per 100 cc. of gastric juice, with an

* Gompertz and Cohen¹¹ have shown that 0.25 mg. of histamin is entirely adequate to provoke a typical acid secretion, and its administration is not accompanied by as undesirable symptoms as the larger doses.

average of 38 cc. The peptic activity varied from 15 to 20 mm. digestion of egg albumen per day. Carlson¹⁴ gives the composition of normal human gastric juice as containing from 40 to 50 cc. N/10 acid per 100 cc. Bloomfield and Keefer¹⁵ have noted the constancy of acid secretion during repeated analyses in the same individual under basal conditions, using the same test stimulus.

Eighteen of the 24 patients showed acid secretion below the normal range during most of the period of gestation. The 24 patients were divided into four groups, according to the degree of reduction of acidity. The first group consisted of 3 patients who had a total and persistent post-histamin achlorhydria with no return of free acid after delivery. The maximum hydrogen-ion activity after histamin in this group was pH 7. Peptic activity of these patients' gastric juice was of a low order, averaging 3.3 mm. digestion of egg albumen per day.

CHART I.—GASTRIC SECRETIONS OF PATIENT 3.*



In the second group were 7 patients who during most of pregnancy secreted gastric juice with a free HCl concentration of less than 10 cc. N/10 acid per 100 cc. after an alcohol test meal. The average maximum was 3.3 cc., with an average total acidity of 12 cc. and an average peptic activity of 6.8 mm. per day. Five of these patients on 18 analyses secreted no free HCl until after histamin had been injected, and 3 secreted no acid after histamin on one or more occasions. Of these 7, 2 showed a return to normal acid secretion and 3 secreted increased, although still subnormal, amounts

* Maximum free HCl and total acidity after alcohol test meals. Following subcutaneous injection of 0.3 mg. histamin, 44, 38 and 26 cc. of N/10 free HCl per 100 cc. of gastric juice were present on the 142d, 177th and 244th days, respectively, when no free HCl was found after alcohol test meals. (In this and subsequent charts the day of delivery is arbitrarily set at 280.)

of acid after delivery. The analyses of Patient 3 (Table 1, Chart I) illustrate the secretions of a case typical of this group. For simplicity in presentation, only the maximum values obtained in any single gastric analysis are shown.

TABLE 1.—TYPES OF GASTRIC SECRETORY RESPONSE DURING PREGNANCY.

Patient No.	Day of pregnancy.	Maximum free HCl.	Maximum total acidity.	Maximum H ⁺ ion activity, pH.	Pepsin, mm. of egg albumen digested per day.
		Within 40 min. of alcohol test meal, cc. N/10 acid per 100 cc.			
3	100	7.0	17.0	2.4	8.0
	142	0.0*	16.0	5.8	8.0
	177	0.0*	7.5	6.0	4.0
	214	2.5	14.5	2.8	5.2
	244	0.0*	8.0	5.4	3.6
	Post-partum . 8	32.0	44.0	1.4	7.8
4	103	21.0	50.0	1.8	5.6
	141	11.5	19.5	2.0	6.0
	208	12.0	23.0	1.8	9.0
	243	27.0	33.5	1.4	10.5
	Post-partum 10	44.0	52.0	1.4	18.0
2	79	45.0	52.5	1.4	7.5
	112	60.0	73.0	1.4	14.0
	143	49.0	63.0	1.4	12.0
	171	50.0	74.0	1.4	19.0
	201	36.0	41.0	1.4	14.0
	227	36.5	46.5	1.4	13.5
	253	84.0	98.0	1.4	16.0
	Post-partum 10	89.0	97.0	1.4	23.0

* Free HCl was present in the gastric secretions of this patient on these three occasions following the injection of histamin.

Eight patients, comprising the third group, secreted gastric juice with a free acid concentration of less than 20 cc. N/10 acid per 100 cc. after the alcohol test meal throughout most of the period of pregnancy. Their average maximum free HCl was 17.8 cc., average maximum total acidity 26.7 cc. and peptic activity 9 mm. per day. Seven of these 8 patients secreted normal amounts of free acid within 10 days after parturition. Analyses of Patient 4 (Table 1, Chart II) illustrate the gastric secretions of a patient characteristic of this group.

The remaining 6 patients, classed in the fourth group, secreted gastric juice after the alcohol meal which was within normal range throughout pregnancy, with an average maximum free HCl of 34.5 cc. N/10 acid per 100 cc., an average maximum total acidity of 45.9 cc. and an average peptic activity of 11 mm. digestion per day. After delivery 5 of these 6 patients showed definitely increased gastric acidity with free HCl, varying from 50 to 90 cc. and averaging 71.4. Patient 2 (Table 1, Chart III) is a typical example of this group.

Seventeen of the 21 patients who did not have persistent anacidity secreted much greater amounts of acid after delivery than they had

CHART II.—GASTRIC SECRETIONS OF PATIENT 4, FOLLOWING ALCOHOL TEST MEALS.

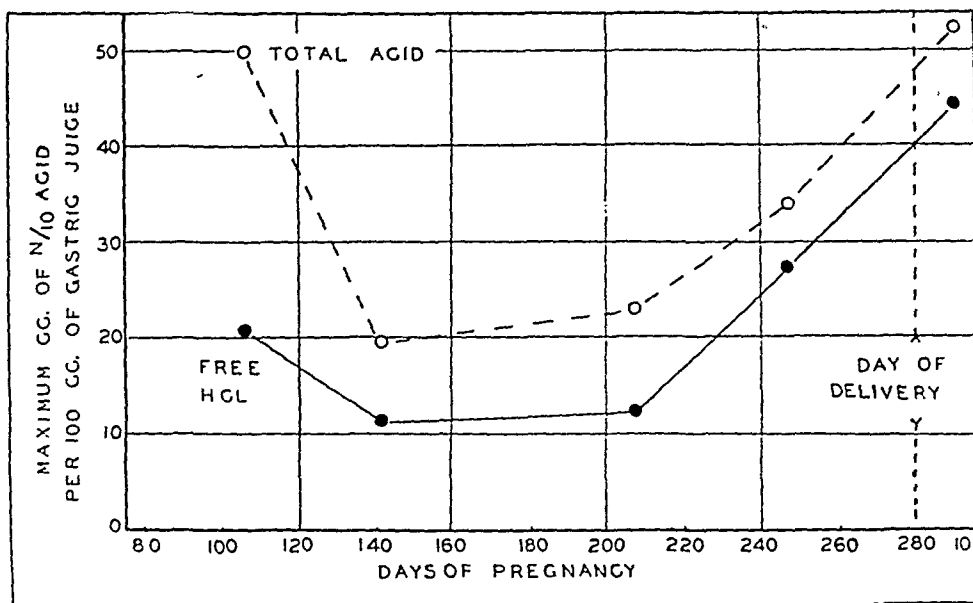
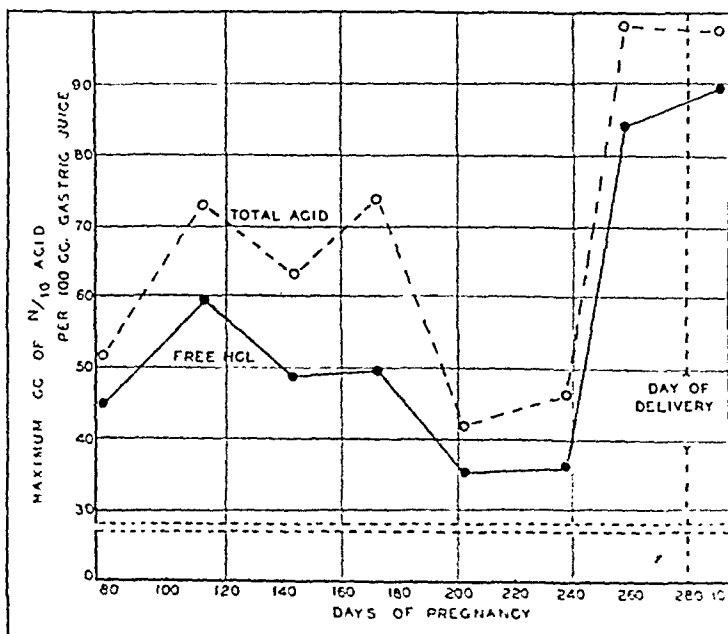


CHART III.—GASTRIC SECRETIONS OF PATIENT 2, FOLLOWING ALCOHOL TEST MEALS.

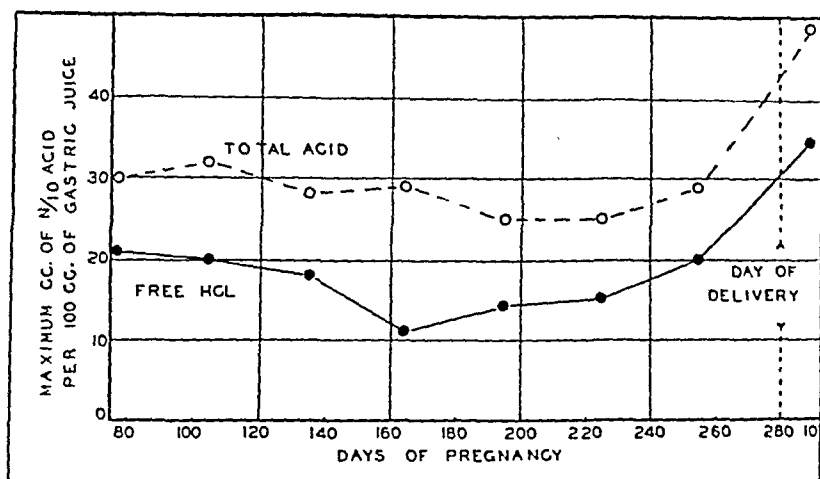


during pregnancy. Since these women were not studied before pregnancy, the condition after pregnancy has been taken as *probably* representative of the gastric secretion before pregnancy. In a few

cases normal acid values were noted early in pregnancy and a number showed a tendency to secrete more acid in the last month than in the earlier months of gestation (Charts II and III).

A composite curve is shown in Chart IV, giving the data for the 21 patients who did not have total acidity. Although not as significant as the individual curves, certain points may be noted. There is a 50 per cent decline in maximum free acidity from the third month to the sixth month of gestation with a rise in the last month to the level observed in the third month. The gastric juice after delivery contains three times as much free acid as during the sixth month and double the quantity secreted during the major portion of pregnancy.

CHART IV.—COMPOSITE CURVE OF GASTRIC SECRETIONS FOLLOWING ALCOHOL TEST MEALS OF 21 WOMEN DURING AND AFTER PREGNANCY.



The curve for total acidity follows in general the curve for free acid which roughly parallels that for the concentration of peptic enzyme.

Discussion. It is a matter of common knowledge that symptoms referable to the upper gastro-intestinal tract are among the most frequent complications of pregnancy. The mechanism of these conditions has never been clearly understood, although recently Alvarez and Hosoi¹⁶ have studied the intestinal tract of pregnant rabbits and have found that the gradient of irritability was flattened in some and reversed in others, and that the rate of rhythmic contraction was generally slowed. The investigations of Nakai and Arzt previously mentioned, together with the data here presented, indicate that there is a decreased secretory power of the gastric mucosa during pregnancy. The nature of the mechanism respons-

ible for this diminution remains obscure. In the nonpregnant individual it is known that fever,¹⁷ injections of foreign protein¹⁸ and artificial tropical climate¹⁹ will depress gastric function. A group of investigators in India²⁰ has compared the *fasting* gastric contents of vegetarian Hindus and of meat-eaters, without detecting any difference between the two. Low chlorid diets have been found to have no influence upon the gastric secretion until late stages of inanition.¹⁴

In our studies no correlation could be obtained between reduction in gastric acidity and the age of the patients, nor did the number of previous pregnancies appear to be of significance.

Although mucus can diminish titratable free acid, the absence of correlation between the amount of mucus present and the free acidity of the specimens, together with the low total acidities observed, indicate that mucus played no rôle in the production of the abnormally low quantities of free acid observed in the gastric contents during pregnancy.

It is known that the regurgitation of duodenal contents may neutralize free acid secreted in the stomach. The absence of bile in almost all of the specimens obtained is evidence against this being a factor in the results observed. Moreover, peptic enzyme values were fairly well correlated with acidity values, suggesting that neutralization from either duodenal contents or mucus was not involved.

From these data it appears that a majority of pregnant women have a significant reduction in the free HCl and total acidity of their gastric juice, accompanied by a parallel reduction in ferment content and hydrogen-ion activity. All but 1 of the 6 patients who had an apparently normal gastric juice during pregnancy had an increased gastric acidity post-partum, suggesting that they also had a reduction of gastric acidity during pregnancy. It is apparent that, unlike the constancy of gastric secretions in repeated analyses upon the same subject noted in nonpregnant individuals,¹⁵ wide variations occur during the course of pregnancy. No correlation between these variations and either morning sickness or vomiting late in pregnancy could be determined.

The importance of altered gastric function that occurs in pregnancy is a matter for consideration from various points of view. Its rôle in inhibiting optimal nutrition may be important, also its possible relation to blood formation as discussed in the following paper.

Summary. 1. Gastric analyses (142) made upon 24 women during pregnancy and the puerperium showed that 75 per cent of the patients did not secrete normal amounts of free HCl or pepsin during more than half of the period of pregnancy.

2. Excluding 3 patients who had persistent achlorhydria even

after histamin injection, 80 per cent of the patients secreted higher concentrations of HCl in the gastric juice after delivery than during pregnancy; the secretion during the puerperium being approximately 3 times as great as that during the sixth month of gestation.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose coöperation this study was made possible.

BIBLIOGRAPHY.

1. Castle, W. B., Heath, C. W., Strauss, M. B., and Townsend, W. C.: The Relationship of Disorders of the Digestive Tract to Anemia, *J. Am. Med. Assn.*, 1931, 97, 904.
2. Eggleston, E. L.: Pathologic Conditions Secondary to Achlorhydria, *J. Am. Med. Assn.*, 1931, 97, 1216.
3. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia and Free Hydrochloric Acid and that of Patients without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *Am. J. Med. Sci.*, 1931, 182, 741.
4. Keefer, C. S., Yang, C. S., and Huang, K. K.: Anemia Associated with Chronic Dysentery, *Arch. Int. Med.*, 1931, 47, 436.
5. Eusterman, G. B., and O'Leary, P. A.: Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-intestinal Tract, *Arch. Int. Med.*, 1931, 47, 633.
6. Mettler, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, *Am. J. Med. Sci.*, 1931, 181, 25.
7. Nakai, T.: On the Gastric Juice of the Pregnant Woman, *Tokio J. Biochem.*, 1925, 5, 465.
8. Arzt, F.: On the Gastric Juice During Pregnancy, *Am. J. Obst. and Gynec.*, 1926, 12, 879.
9. Idem: Further Observations on the Gastric Juice in Pregnancy, *Ibid.*, 1930, 20, 382.
10. Mason, L. W.: Gastric Acidity in Pregnancy, *Colorado Med.*, 1931, 28, 392.
11. Gompertz, L. M., and Cohen, W.: The Effect of Smaller Doses of Histamin in Stimulating Human Gastric Secretion, *Am. J. Med. Sci.*, 1929, 177, 59.
12. Hammarsten, O., and Hedin, S. G.: *A Textbook of Physiological Chemistry*, New York, John Wiley & Sons, 1914.
13. Clark, W. M.: *The Determination of Hydrogen Ions*, Baltimore, The Williams & Wilkins Company, 1923.
14. Carlson, A. J.: The Secretion of Gastric Juice in Health and Disease, *Physiol. Rev.*, 1923, 3, 1.
15. Bloomfield, A. L., and Keefer, C. S.: Clinical Physiology of the Stomach, *Arch. Int. Med.*, 1926, 38, 145.
16. Alvarez, W. C., and Hosoi, K.: Reversed Gradients in Bowel of Pregnant Animals, *Am. J. Obst. and Gynec.*, 1930, 19, 35.
17. Meyer, J., Cohen, S. J., and Carlson, A. J.: Contribution to the Physiology of the Stomach: XLVI. Gastric Secretion during Fever, *Arch. Int. Med.*, 1918, 21, 354.
18. Meyer, J., and Kartoon, L. B.: The Effects of Intravenous Injections of Foreign Protein on Peptic Ulcer, *Arch. Int. Med.*, 1930, 46, 768.
19. Borchardt, W.: Die Magenfunktion im künstlichen Tropenklime (Nach Versuchen an Tieren und Menschen), *Klin. Wchnschr.*, 1930, 9, 886.
20. Bhatia, S. L., Patel, H. S., and Dundas, J. D.: Studies in Gastric Secretion. Part I, *Ind. J. Med. Res.*, 1931, 19, 259.

STUDIES OF ANEMIA IN PREGNANCY.

II. THE RELATIONSHIP OF DIETARY DEFICIENCY AND GASTRIC SECRETION TO BLOOD FORMATION DURING PREGNANCY.

BY MAURICE B. STRAUSS, M.D.,

AND

WILLIAM B. CASTLE, M.D.,

BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital; the Departments of Medicine and Tropical Medicine, Harvard Medical School.)

THE occurrence of anemia during the progress of pregnancy has long been a matter of common observation. Bland, Goldstein and First¹ have recently reviewed the literature and published a bibliography of 56 references up to 1929. Since then several other papers have appeared.²⁻¹⁰ A survey of the literature suggests a number of hypothetic causes of this anemia, but fails to reveal evidence confirming any one of them. It has been well established that the anemia is most marked in the early part of the last trimester of pregnancy, and that there is some slight tendency to spontaneous recovery in the last month or two immediately preceding delivery. The absence of correlation between the degree of the anemia and the age, parity or blood pressure of the patients has been noted.¹ Focal infection, toxemia and syphilis have not been found to play a significant rôle.¹

In the absence of a satisfactory explanation for the reduction in both erythrocytes and hemoglobin these phenomena have been termed "physiologic anemia of pregnancy" and considered normal. Marked degrees of this physiologic anemia of pregnancy resemble the anemias associated with gastro-intestinal disturbances, poor diet and chronic blood loss. An investigation of these three factors in 22 pregnant women without demonstrable disease, who applied for routine prenatal care, was, therefore, made in order to throw light upon the mechanism of anemia in pregnancy.

Methods. Complete measurement of gastro-intestinal function should include a study, not only of the contents, but also of all of the known enzymes, and those of the accessory glandular organs, as well as observations on the absorptive capacity and motility of the bowel. The difficulty of such a task led us to choose a measure of gastric secretory function which could easily be determined at monthly intervals and might serve as an index of general gastro-intestinal function, namely, the ability of the stomach to secrete acid. Previous studies¹¹ have shown that, while defects of gastric secretion may occasionally be present without disturbance of acid secretion, in general a fair degree of correlation exists between the latter and other gastric secretory functions. Gastric analyses were performed at monthly intervals and after delivery as described in the preceding paper.¹²

The determination of a patient's diet over a period of years requires painstaking inquiry, but it was found possible to formulate a fairly definite concept of the patient's dietary habits from repeated and careful questioning. Careful histories were taken of the usual food intake of these patients for the years before and during pregnancy, and notes made of any disturbances during pregnancy, such as nausea or vomiting, which might interfere with the diet, either as to quality or quantity. The diets of none of the 22 patients were found defective in total calories, as evidenced by the description of the diets themselves and as inferred from the normal gain in weight exhibited by all. In no instance was there any apparent fat, carbohydrate or vitamin deficiency. Wide variations, however, occurred in the consumption of protein foods, fruits and green vegetables. The range extended from 1 patient who ate no meat, fish or eggs throughout pregnancy, and fruit and vegetables not more than once a week during and before pregnancy, to a patient who ate meat, fruit, vegetables and eggs twice daily. For purposes of classification, any patient who ate meat, fruit and vegetables less than three times a week was considered to have a poor diet, and the remainder considered to have a reasonably suitable diet, although probably few partook of diets that could be considered optimal. Most of these individuals ate meat, fruit and a vegetable at least once daily. The outstanding characteristic of the poor diets was the lack of iron and related mineral salts and the low protein intake.

To eliminate the effects of blood loss no patient giving a history of hemorrhage of any kind or menorrhagia was studied. However, since the fetal blood and muscle pigment-building materials are derived entirely from the maternal organism, it is conceivable that repeated pregnancies might produce the same effects as chronic blood loss. While it is possible also that the normal bleeding at delivery, if repeated many times, might represent chronic blood loss. Yet; if either of these possibilities is true there should be some correlation between the blood level and the number of pregnancies.

The blood was examined every month until the last month of pregnancy, then every 2 weeks until delivery, and on the first day after delivery, on the fifth or sixth, on the eighth to tenth day, and again 3 months after parturition. All determinations were made upon venous blood uniformly drawn without stasis from the antecubital vein. The diluting pipettes and counting chambers used were certified by the U. S. Bureau of Standards. The hemoglobin was determined by the Sahli method, with tubes calibrated so that 100 per cent equalled 15.6 grams of hemoglobin per 100 cc. of blood.

To determine the average ranges of the hemoglobin and erythrocyte concentration during and after pregnancy, and to furnish sufficient data to correlate blood levels with age and parity of the patients, 200 blood examinations were made upon an unselected group of 200 pregnant women, distributed equally in the last 8 months of pregnancy, 1 and 10 days post-partum.

Results. Two of the patients who were followed throughout pregnancy were definitely anemic when first seen. The remaining 20 were divided into four groups. The patients of the first three groups all had good diets.

Nine patients composed the first group and had throughout pregnancy 15 cc. or more N/10 free HCl per 100 cc. of gastric juice.¹² The 3 patients in the second group had less than this amount, and the 3 in the third group had total achlorhydria (*i. e.*, after injection of histamin). There were 5 patients in the fourth group, all of

whom had poor diets and less than 15 cc. of N/10 free HCl per 100 cc. of gastric juice.

The hemoglobin determinations on Group I, comprising the 9 patients whose gastric secretion contain 15 cc. or more N/10 HCl throughout most of pregnancy and who ate adequate diets, are shown in Chart I. Only 1 of these patients had below 60 per cent of hemoglobin at any time during pregnancy. The average difference between the highest and lowest determination in any month in this group was less than 14 per cent. Within 10 days after delivery all but 1 patient had between 73 and 84 per cent of hemoglobin. No significant change was found 3 months later. The average hemoglobin curve for this group (Chart IV) showed a 5 per cent loss from the third month of pregnancy to the tenth day post-partum.

Chart II represents the hemoglobin determinations on the second group composed of the 3 patients with less than 15 cc. of N/10 free HCl who had satisfactory diets. One of these patients had had an exceptionally good diet* throughout pregnancy and showed a hemoglobin curve which corresponded to the curves of the first group. The other 2, who took the average diet, had hemoglobins of 63 and 70 per cent, respectively, 10 days post-partum. Both had below 60 per cent during part or all of the third trimester of pregnancy. An average loss of 9 per cent hemoglobin occurred between the third month of pregnancy and the tenth day post-partum.

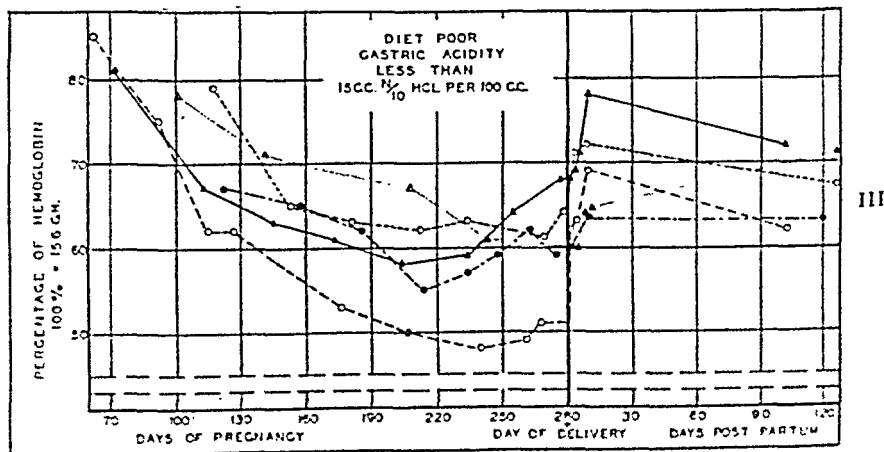
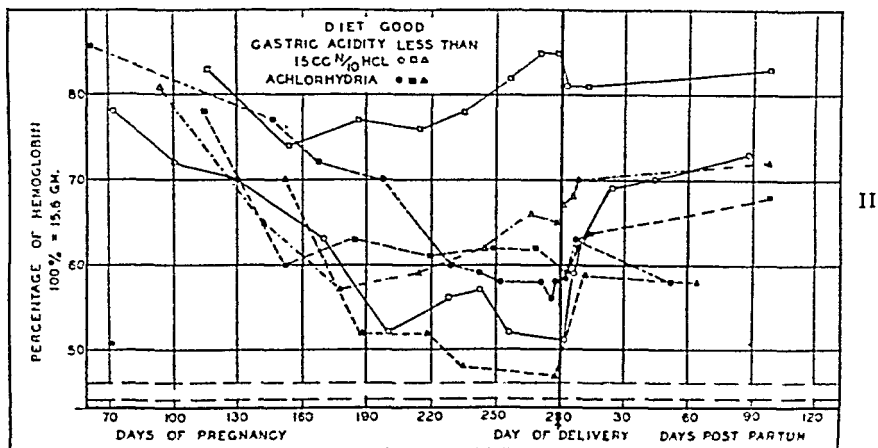
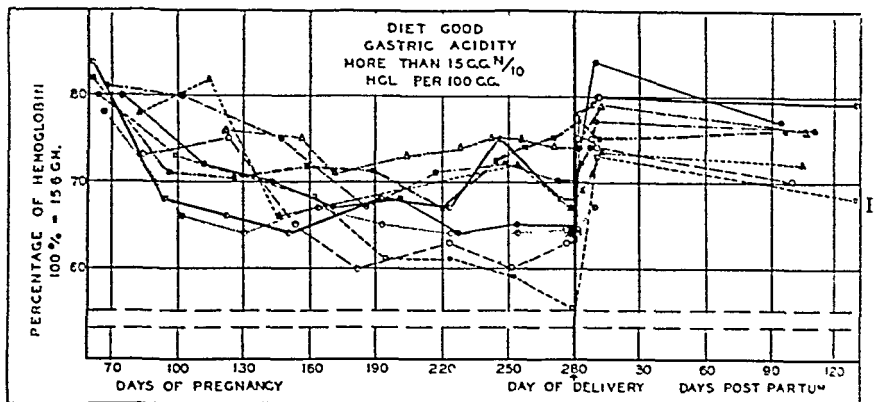
The third group of 3 patients had a total achlorhydria (after histamin injection) and had diets which were considered comparable to those of the individuals comprising the first two groups. The curves representing their hemoglobin determinations (Chart II) show low points of 58, 56 and 47 per cent during pregnancy, levels of 64, 63 and 59 per cent 10 days post-partum and no subsequent improvement 3 months later. The average loss of hemoglobin in this group during pregnancy was 18 per cent.

The 5 patients in Group IV had less than 15 cc. of N/10 free HCl, and took distinctly unsatisfactory diets. The low points reached by the hemoglobin during pregnancy (Chart III) were 48, 55, 58 and 61 per cent, respectively, with a return to an average of 69 per cent 10 days after delivery without further change of significance within the next 3 weeks. The average loss in this group was 14 per cent of hemoglobin.

For comparison, the average curves of 3 of the groups have been plotted in Chart IV. (Group II has such a wide dispersion in hemoglobin values for the 3 cases as to make an average curve of little significance.) All 3 groups recorded in Chart IV had an average hemoglobin of 80 per cent in the third month of pregnancy. Until the end of the sixth month there was less than 5 per cent varia-

* Eggs, 2 daily; meat, twice daily; fruit, 2 to 3 times daily; 3 to 4 helpings of vegetables daily.

CHARTS I, II, III.—HEMOGLOBIN DETERMINATIONS OF 20 WOMEN DURING AND AFTER PREGNANCY.



tion between them. However, in the last trimester the group of 9 patients with good diets and more than 15 cc. N/10 free HCl showed a slight gain of hemoglobin, whereas both the group with achlorhydria and the group with poor diet continued to decline, the former to a slightly greater degree than the latter. Ten days post-

CHART IV.—ARITHMETIC AVERAGE HEMOGLOBIN CURVES OF 17 PREGNANT WOMEN GROUPED ACCORDING TO DIET TAKEN AND AMOUNT OF GASTRIC HYDROCHLORIC ACID.

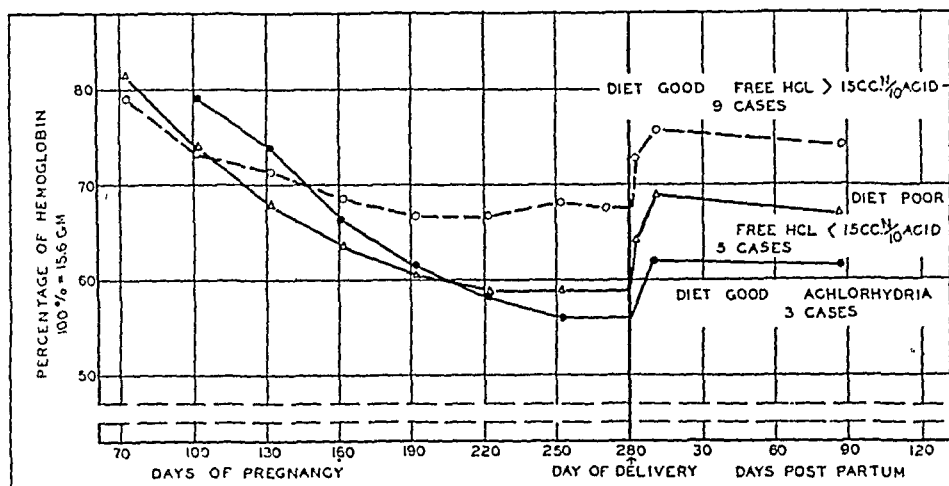
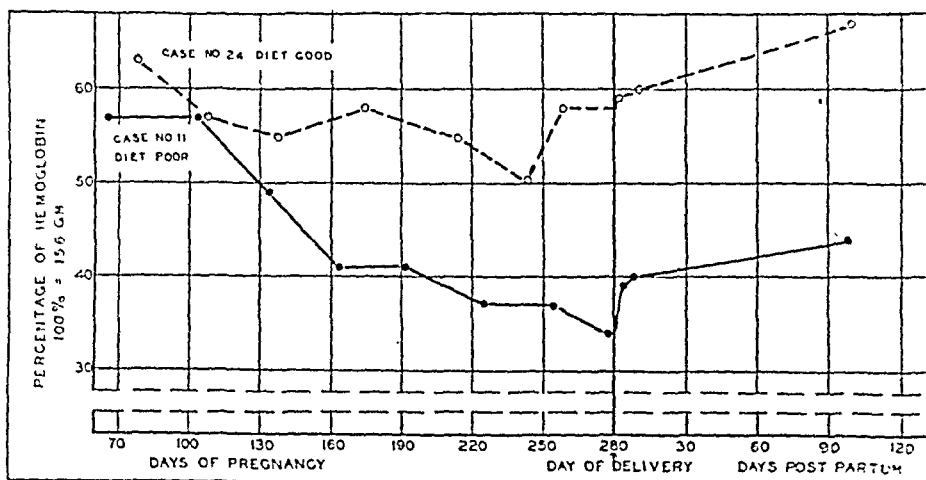


CHART V.—HEMOGLOBIN DETERMINATIONS OF 2 PREGNANT WOMEN DISTINCTLY ANEMIC AT THE ONSET OF PREGNANCY, 1 TAKING A POOR DIET, THE OTHER A GOOD DIET.



partum the hemoglobin of the first group averaged 76 per cent, of the group with poor diet 69 per cent, and of the group with achlorhydria 62 per cent. Three months later no significant changes had occurred, and the latter two groups continued to have on the average less than 70 per cent of hemoglobin.

Data for the 2 cases (11 and 24), which were distinctly anemic when first seen early in pregnancy, are shown separately in Chart V. Both patients had taken inadequate diets throughout their lives. Both had gastric acidity during pregnancy of less than 15 cc. N/10 free HCl. Patient 24, however, began at the onset of pregnancy to eat much meat, fruit and green vegetables, and continued to do so. Patient 11 continued with her previous very unsatisfactory diet throughout pregnancy and thereafter. During the first 5 months of pregnancy, 3 separate hemoglobin examinations of each of the 2 patients showed a maximum difference of 6 per cent. During the last 4 months a progressive divergence of the curves occurred, so that in the first week post-partum the patient who had taken a good diet during pregnancy had a hemoglobin of 60 per cent, whereas the second patient's hemoglobin was 20 per cent lower. Three months later this difference was maintained.

These data show that of the 3 groups of patients who took the better diets the average hemoglobin loss in pregnancy was 5 per cent for the group with higher gastric acidity, 9 per cent for the group with low acidity and 18 per cent for the group with total achlorhydria. For the group of patients with both low acidity and inadequate diets the hemoglobin loss was 14 per cent.

The erythrocyte counts of the 20 patients followed throughout pregnancy and the 200 isolated counts made upon different subjects in the various months of pregnancy (Chart VI) show no essential difference in the general distribution of the two groups or in their arithmetic average curves. This was considered presumptive evidence that the blood changes of the smaller group were fairly typical of those of pregnant women generally. The data presented in Chart VI show a difference of about 2 million red blood cells per c.mm. between the highest and lowest counts in any 1 month. Hence, the average curve, with its maximum variation of 0.8 million cells per c.mm., has little claim to validity upon statistical grounds. However, since the 20 individual curves of separate subjects all follow the same general contour, it is simpler to present only the average curves. It will be noticed that a steady decline of erythrocytes occurred, with the lowest counts usually at the end of the second trimester. There was then an average increase of 0.25 million cells per c.mm. in the last trimester and within a week after delivery the number of erythrocytes suddenly increased about 0.5 million to an average of 4.5 million per c.mm.

The results of 200 hemoglobin determinations throughout pregnancy and after delivery show (Chart VII) an average variation of 30 per cent between high and low values in any 1 month. The average curve is presented for comparison with the curves of Charts I and IV. It shows a progressive decline during the first 2 trimesters of pregnancy followed by a rather stationary course until delivery and then a sudden gain of 5 per cent. These curves are in essential agreement with those of Kühnel.¹²

CHART VI.—ERYTHROCYTE COUNTS ON 200 DIFFERENT WOMEN IN DIFFERENT MONTHS OF PREGNANCY AND IN THE PUERPERIUM (OPEN CIRCLES) AND 220 ERYTHROCYTE COUNTS ON 20 PATIENTS THROUGHOUT PREGNANCY AND AFTER (SOLID DOTS). THE ARITHMETIC AVERAGE CURVE OF THE OPEN CIRCLES IS SHOWN BY THE SOLID LINE; OF THE SOLID DOTS BY THE BROKEN LINE.

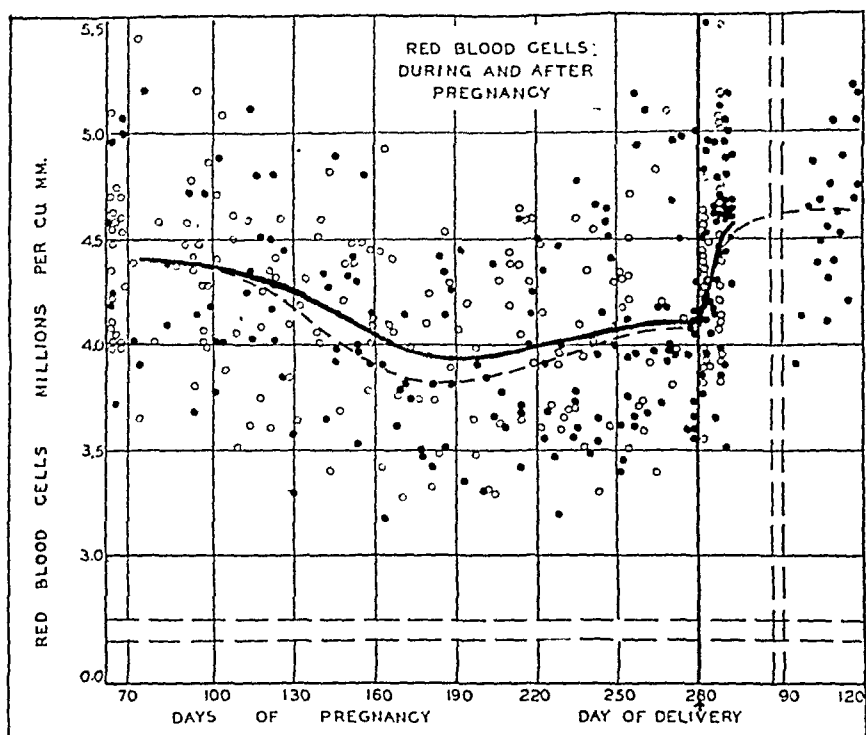
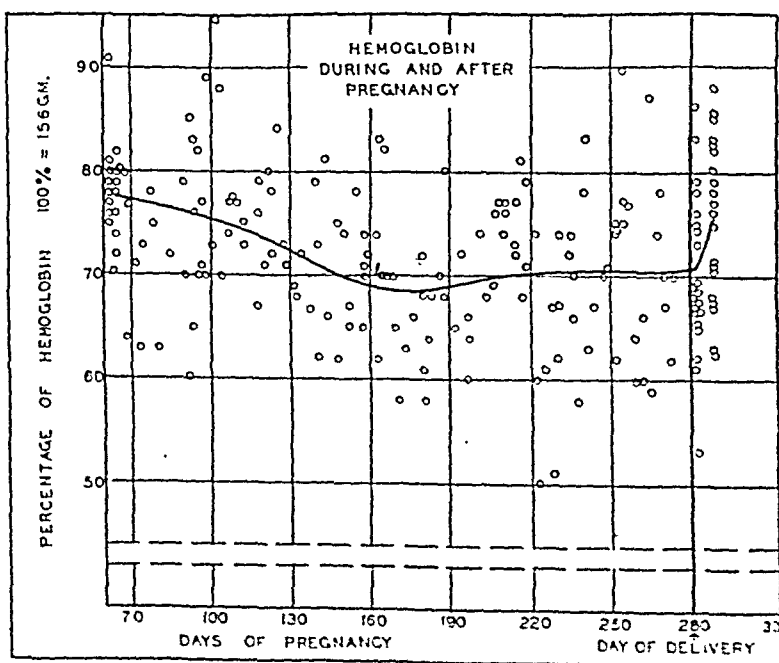


CHART VII.—HEMOGLOBIN DETERMINATIONS ON 200 WOMEN IN DIFFERENT MONTHS OF PREGNANCY AND IN THE PUERPERIUM.



Correlating the erythrocyte counts and hemoglobin determinations with the number of pregnancies and with the age of the patient, the averages for the patients in their third to fourteenth pregnancy were found to be the same as in those having their first or second child. The average age of all of the patients was 26 years; the average erythrocyte and hemoglobin concentration of the patients 26 years of age or over was the same as for those below 26 years.

Discussion. The data obtained from the examination of the blood of 200 women in the different months of pregnancy serve to illustrate the wide variations which may occur at any one time in pregnancy. The similarity of distribution of points representing the small group of patients followed from month to month, and those of the larger group of 200 cases, indicates that the small group was a fair sample of all pregnant women attending the Out-Patient Department. Further, the entire absence of correlation between age or parity and blood levels rules out the possible etiologic influence of these factors in producing variations in the degree of anemia in pregnancy.

Since the average curve for erythrocytes during pregnancy is roughly typical of the individual curves, the significance of the changes may properly be discussed. The most striking feature was the gain of approximately 500,000 mature red blood cells per c.mm. within 1 week after parturition. The rapidity of this gain is evidence that it is not entirely the result of increased blood formation. The question arises as to whether it is not merely an increased concentration due to a loss of plasma. The effect of dehydration in producing a concentration of the cellular elements of the blood is well known. Keith, Rowntree and Geraghty¹⁴ have found that the average blood volume of women decreases 1100 cc. within 7 to 10 days after delivery. Only 300 cc. of this decrease may be ascribed to bleeding during parturition, the remaining 800 cc. representing loss of plasma volume. Their studies of whole blood and plasma volume corroborate the fact that it is chiefly the plasma volume which is reduced. This reduction in plasma without change in cells must affect the concentration of the cells according to the formula:

$$\text{Post-partum erythrocyte concentration} = \text{ante-partum erythrocyte concentration} \times \frac{\text{ante-partum blood volume}}{\text{post-partum blood volume}}$$

Substituting our data for ante-partum erythrocyte concentration and the quoted figures for blood volume:

$$\text{Post-partum erythrocyte concentration} = 4,050,000 \times \frac{5.876}{5.076} = 4,680,000 \text{ erythrocytes per c.mm.}$$

which corresponds closely to our observed values post-partum. Hence, it is reasonable to believe that the return of erythrocytes to

normal levels post-partum was due largely to a return of the blood volume to normal amounts and, conversely, that the decrease in erythrocyte concentration observed in the first six months of pregnancy was mainly due to the increasing blood volume. That the increase of plasma volume does occur in the first half of pregnancy rather than later is evidenced by the work of Bohnen and Borrmann.¹⁵ However, carefully correlated studies of blood volume and cell concentration must be performed before this hypothesis can be accepted.

Two other theories may be mentioned at this point. The first, that a toxic hemolysin is produced by the fetus or placenta,^{16,17,18} is unsound, since there is no evidence that such a factor exists or that there is increased hemolysis under the conditions of normal pregnancy. The second, that toxic inhibition of the bone marrow occurs, lacks, in the first place, evidence for the existence of a toxin; second, evidence of inhibition of the leukocytes¹⁹ such as is found in other types of toxic action on the bone marrow; and third, evidence that the hemoglobin returns to normal during the 3 months after delivery when the toxic factor should no longer be present.

Assuming that the changes occurring in hemoglobin and erythrocyte concentration during the first half of pregnancy and in the week post-partum are due to plasma volume changes, it is to be observed that the actual differences in hemoglobin concentration in different patients manifest themselves during the *last* half of pregnancy. This is the period during which the fetus is laying down its chief supply of blood-building materials,^{20,21,22} which must of necessity be derived from the maternal organism. In this respect it is significant that the babies of the 22 women studied all had normal erythrocyte counts and hemoglobin values. A reasonable hypothesis would thus be that the cause of anemia beyond a degree attributed to alteration of plasma volume in the mother lies in an inadequate supply of these building materials to meet both the fetal and the maternal demand.

In the absence of complications such as hemorrhage the factors that may reasonably be considered to influence the maternal supply of hemoglobin building materials are two: (1) The amount of such material taken in as food; (2) the absorption of such material after ingestion, or utilization after absorption. Studying the 20 cases from the point of view of food intake and of gastric acidity (as a measure of gastro-intestinal function²³), there were 9 patients with both of these factors normal. In these patients no significant anemia occurred.

Of the 3 patients with a normal diet but with total achlorhydria, on the other hand, all developed a moderately severe grade of anemia during pregnancy, and 10 days post-partum their average hemoglobin was 62 per cent as compared to 76 per cent for Group I mentioned above. The 5 patients who had poor diets and moderate reduction in gastric acidity showed the development of moderate

anemia with an average 10-day post-partum hemoglobin of 69 per cent. Two patients with moderate reduction in gastric acidity, and diets as satisfactory as commonly taken, showed less anemia than those individuals with poor diets, and, furthermore, during the first 3 months post-partum, when their gastric juice had returned to normal, they had a progressive gain in hemoglobin. A third patient who had an unusually satisfactory diet, failed to develop any appreciable anemia.

The existence of anemia prior to the beginning of pregnancy apparently need not condition anemia of greater degree during pregnancy. This is illustrated by the course of the 2 patients mentioned above, both of whom had a moderate anemia associated with inadequate diets before they became pregnant. The one who continued to eat poorly became severely anemic during pregnancy while the other, who ate well from the beginning of pregnancy, actually gained hemoglobin during the course of her pregnancy.

The anemia of these pregnant women thus differed in no distinctive way from anemia associated with chronic blood loss, poor diet or gastric anacidity. In these patients the demands of the fetus for hemoglobin-building materials represented blood loss just as definitely as would menorrhagia, and pregnancy depressed the gastric acidity even in those patients who later showed normal values. The type of dietary deficiency (low intake of protein, iron and perhaps other metals) encountered in some of these patients with anemia is the same as that noted by Mettier and Minot,²³ and others in patients with hypochromic anemia, and the rôle of gastric anacidity in the production of this type of anemia has been repeatedly emphasized.^{8,23,24,25,26,27} In short, then, in pregnancy the combination of the loss of blood-building materials to the baby, the lowering of the gastric acidity and, in many cases, the alteration of the diet of the patient, produces anemia by the same mechanisms that produce similar types of anemia in the nonpregnant individual.

Conclusions. 1. Anemia in pregnancy (reduction in the total hemoglobin content of the mother's blood) occurs during the last trimester of pregnancy when the fetus draws upon the maternal organism for blood-building, muscle-building and storage materials and is found only in those patients who have had for a considerable time a defective diet or dietary deficiencies conditioned by gastric anacidity or related gastro-intestinal disturbances.

2. The "physiologic" reduction of erythrocytes during pregnancy is probably due to hydremia and is not a true anemia.

3. These observations suggest the importance of an optimal diet and one especially rich in proteins and iron-containing foods for the prevention of anemia in pregnancy.

It is a pleasure to acknowledge our indebtedness to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose cooperation this study was made possible.

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BIBLIOGRAPHY.

1. Bland, P. B., Goldstein, L., and First, A.: Secondary Anemia in Pregnancy and in Puerperium, *Am. J. Med. Sci.*, 1930, **179**, 48.
2. Pepper, O. H. P.: A Review of Our Knowledge of the Anemias of Pregnancy, *Med. Clin. North America*, 1929, **12**, 925.
3. Bland, P. B., Goldstein, L., and First, A.: The "Physiological" Anemia of Pregnancy, *Surg., Gynec. and Obst.*, 1930, **40**, 954.
4. Nalle, B. C.: Anemia of Pregnancy, *South. Med. J.*, 1930, **23**, 490.
5. Moore, J. H.: Anemia in Pregnancy, *Am. J. Obst. and Gynec.*, 1930, **20**, 254.
6. Jerlov, E.: Hemoglobin Deficiency in Pregnancy and a Suggestion for the Prophylaxis of Anemia, *Acta Obstet. et Gynecol.*, 1929, **8**, 356.
7. Galloway, C. E.: Anemia of Pregnancy, *J. Am. Med. Assn.*, 1929, **93**, 1695.
8. Strauss, M. B.: Chlorotic Anemia of Pregnancy, *Am. J. Med. Sci.*, 1930, **180**, 818.
9. Yang, C. S., and Keefer, C. S.: The Anemias of Pregnancy, *Nat. Med. J. China*, 1930, **16**, 159.
10. Wills, L., and Mehta, M. M.: Studies in "Pernicious Anemia" of Pregnancy, *Ind. J. Med. Res.*, 1930, **17**, 777. Wills, L., and Talpade, S. K.: *Ibid.*, 1930, **18**, 283. Wills, L.: Treatment of "Pernicious Anemia of Pregnancy" and "Tropical Anemia" with Special Reference to Yeast Extract as a Curative Agent, *Brit. Med. J.*, 1931, **i**, 1059.
11. Castle, W. B., Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *IV*, *Am. J. Med. Sci.*, 1931, **182**, 741.
12. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy. I. Gastric Secretion in Pregnancy and the Puerperium, *Am. J. Med. Sci.* (preceding article).
13. Kühnel, P.: Untersuchungen über die physiologische Schwangerschaftsanämie, *Ztschr. f. Geburtsh. u. Gynäk.*, 1926, **90**, 511.
14. Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volumes, *Arch. Int. Med.*, 1915, **16**, 547.
15. Bohnen, P., and Borrmann, K.: Untersuchungen über die Vermehrung der Blutmenge in der Schwangerschaft, *Arch. f. Gynäk.*, 1925, **126**, 144.
16. Hofbauer, J.: Für die placentare Theorie der Eklampsie-Ätiologie, *Zentralbl. f. Gynäk.*, 1908, **32**, 1469; Die Ätiologie der Eklampsie, *Ibid.*, 1918, **42**, 745.
17. Allan, W.: Hemolytic Anemia in Pregnancy, *Surg., Gynec. and Obst.*, 1928, **47**, 669.
18. Suwa, Y.: Hematologic Investigation of Anemia in Pregnancy, *Japanese J. Obst. and Gynec.*, 1930, **13**, 583.
19. Unpublished data.
20. Hoogounenq, L.: Recherches sur la statique des éléments numeraux et particulièrement du fer chez le fœtus humain, *Compt. rend. Acad. d. sc.*, 1899, **128**, 1054.
21. Zeidberg, L. D.: A Quantitative Determination of the Changes in Hemoglobin Concentration, Volume of Red Cells and Basophilia in the Blood of Rabbit Fetuses at Various Stages During the Last Third of Pregnancy, *Am. J. Physiol.*, 1929, **90**, 172.
22. Smythe, C. V., and Miller, R. C.: The Iron Content of the Albino Rat at Different Stages of the Life Cycle, *J. Nutrition*, 1929, **1**, 209.
23. Mettler, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, *Am. J. Med. Sci.*, 1931, **181**, 25.
24. Faber, K.: Achylia Gastrica mit Anämie, *Med. Klin.*, 1909, **5**, 1310; Anämische Zustände bei der Chronischen Achylia Gastrica, *Berl. klin. Wehnschr.*, 1913, **1**, 958.
25. Witts, L. J.: Simple Achlorhydric Anaemia, *Guy's Hosp. Repts.*, 1930, **80**, 253.
26. Waugh, T. R.: Hypochromic Anemia With Achlorhydria, *Arch. Int. Med.*, 1930, **47**, 71.
27. Davies, D. T.: Studies on Achlorhydria and Anaemia, *Quart. J. Med.*, 1931, **24**, 447.

THE OCCURRENCE OF SICKLEMIA IN THE WHITE RACE.

BY SAMUEL ROSENFELD, M.D.,

ASSISTANT ATTENDING PHYSICIAN; ASSISTANT PATHOLOGIST IN HEMATOLOGY,

AND

JOSEPH B. PINCUS, M.D.,

ASSOCIATE ATTENDING PEDIATRICIAN,

BROOKLYN, N. Y.

(From the Department of Pathology, Dr. Max Lederer, Director, and the Department of Pediatrics of the Jewish Hospital of Brooklyn.)

It is generally believed that the presence of sickle cells in the blood occurs only in the negro race or in those with an admixture of negro blood. This belief is based on reports of numerous examinations for sickle cells in the bloods of both colored and white persons either normal or diseased. The incidence of the sickling trait among unselected negroes seems to be about 7 per cent, as determined by averaging the various figures by writers on the subject.

Sickling of the red blood cells or sicklemia (a term used to designate such a condition of the blood) is not in itself a manifestation of disease, since it can be found in perfectly healthy individuals who never have had anemia. It is a constitutional abnormality of the erythrocytes, probably traceable to a defect in their formation in the bone-marrow. The trait, which is hereditary and transmitted as a dominant character, according to the Mendelian law, is manifested by the transformation of normal round red cells into crescentic or sickle-like structures with pointed or filamentous ends. This transformation is best observed in a sealed wet preparation, wherein the process progressively increases in degree with the passage of time, until a maximum for a particular case has been reached. After the lapse of a certain period of time, varying from several days to 2 weeks, the distorted cells in the wet preparations usually return to their original round appearance. At any time during the period of sickling the affected cells may revert to their normal shape if the cover slip be removed from the wet preparation. When the process of sickling is incomplete, the cells appear shaped like oat or caraway seeds. Stained blood smears may show no characteristic sickling, or may show it in slight and often incomplete degree; rarely do they show the sickling to the degree seen in corresponding sealed wet preparations.

In a small proportion of cases with sicklemia the affected red blood cells are attacked and destroyed by the cells of the reticulo-endothelial system, especially by those of the spleen; and a hemolytic type of anemia results. The term "sickle-cell anemia" is applied to this form of anemia. Although Herrick¹ in 1910 was the first to report the presence of sickle cells in a case of severe anemia, it is to Sydenstricker^{2,3} and to Huck⁴ that we owe most of our knowl-



FIG. 1.—Patient's blood in a sealed wet preparation after 24 hours. (No. 138193.)



edge of sickle-cell anemia as a clinical entity. Comprehensive reviews of the subject have been published by Graham and McCarty⁵ and by Steinberg.⁶

The marked resemblance of sickle-cell anemia to congenital hemolytic icterus has been noted by a majority of writers on the subject. Among the important differences, aside from the sickling of the red blood cells, are the existence of macrocytosis in the stained smears and an increased resistance of the erythrocytes to hypotonic salt solution in sickle-cell anemia, whereas in congenital hemolytic icterus there is microcytosis and a decreased resistance. These differences proved to be of utmost value in the recognition of the case of sickle-cell anemia reported in this paper.

From the ethnologic view-point there is great interest in the question as to whether sickle cells ever occur in white persons in whom there is no suspicion of admixture of negro blood. In the literature there is much confusion on this point, which is chiefly one to mistaking other deformities of the red blood cells for sickling or to a strong suspicion of admixture of negro blood in cases with true sickling.

Analysis of the literature with these possibilities in mind has resulted in the elimination of most of the cases from the category of sickle-cell anemia in a white person.

The first report of sickle-cell anemia in a white person is that of Castana⁷ in 1925. In eliminating this case there are several points to be considered. In the first place, there are no illustrations. Second, there is no mention of the behavior of the patient's red cells in sealed wet preparations, an essential test in determining sickling. Third, and most important, is the fact that Castana's description of the semilunar or sickle-like gigantocytes and his references to these cells by other authors definitely identify them as "*corps en demi-lune*" of the French. Such cells represent degenerative erythrocytes and not true sickle cells. More recently they have been described by Schilling⁸ and by Lambin and Leto.⁹

In 1926 a second case of sickle-cell anemia in a white person was reported by Archibald.¹⁰ This was a typical case of sickle-cell anemia, illustrated by convincing photographs, in an Arab boy, aged 2 years, a native of the Sudan, Africa. The parents were both Arabs, and their blood showed no evidence of sickling. Nothing is stated of the possible presence of negro blood in the family tree, nor is any mention made regarding the appearance of the features of the patient or of his parents. Since the residence of the patient is in a region where the inhabitants are predominantly negro and where interbreeding is notoriously common, the probability of an admixture of negro blood in this case is very strong. For this reason this case cannot be regarded strictly as one of sickle-cell anemia in a white person who is free of the suspicion of an admixture of negro blood.

The third case, reported by Stewart,¹¹ was in an apparently white child, aged 6 years, with the facial characteristics of a negro—features of an octaroon, kinky hair, thick lips, and a flattened nose. The father was a healthy white man with no sickling in his blood and without any negro characters. The mother, who showed sickle cells in her blood, although considered a white person by her neighbors, had a dark skin and the features of a Cuban, and was of Cuban descent. It is well known that Cuba is a violent melting pot, with the negro the predominant type. Moreover, the family lived in a district bordering on the colored section. For these reasons this case also cannot be regarded strictly as within the category of sickle-cell anemia in a white person.

In 1927 Lawrence¹² reported elliptical and sickle-shaped erythrocytes in the blood of 6 white patients, and believed he was dealing with the sickle-cell trait. The photomicrographs, however, showed not the morphologic characteristics of true sickle cells, but a peculiar anomaly of the erythrocytes, wherein the latter have a constant elliptical form. In a later paper¹³ Lawrence included the above cases as examples of the presence in the blood of elliptical erythrocytes and not of sickle cells.

In 1929 Cooley and Lee¹⁴ reported a case of sickle-cell anemia in a white child of Greek descent. The description of the case and the photographs of the blood are convincing. This case we regard as the first one of sickle-cell anemia in a white person, in whom no reasonable suspicion can be raised of an admixture of negro blood.

In 1931 Sights and Simon¹⁵ described a case of erythrocytic sickling with anemia in a white native American of Scotch-Irish parentage. The absence of a racial and geographical study of other members of the patient's family to exclude the possible admixture of negro blood decreases considerably the value of this case from an ethnologic viewpoint.

The following case is considered the third one of sickle-cell anemia in a white person where no evidence of admixture of negro blood can be discovered.

Case Report. M. Y. (No. 138193), a boy, aged 9 years, was admitted to the Jewish Hospital on April 9, 1931, on the service of Dr. B. Kramer. His chief complaint was intermittent attacks of abdominal pain for the past 5 years.

Family History. The father, who died 5 years ago, was born in the town of Reggio, Calabria, which is in southern Italy, where his family lived for generations and where negroes are unknown. A brother of his, whose blood shows no sickle cells, is certain that his parents and grandparents had no negro features. The mother of the patient, whose blood shows sickle cells and who as a child was anemic and in poor health, was born in the United States, where she has lived her entire life. She has a muddy complexion, but she has no features suggestive of the negro. She has 2 children, of whom 1 is the patient. The other child is a girl, aged 12 years, who has no feature suggestive of the negro and has sickle cells in her blood. The mother has 3 sisters and several brothers, none of whom shows anything suggestive of

TABLE 1.—BLOOD STUDIES IN THE CASE OF SICKLE-CELL ANEMIA IN A WHITE CHILD.

Date.	Hemoglobin per cent (Dare).	Erythrocytes millions per c.mm.	Color index.	Platelets thousands per c.mm.	Leukoocytes thou- sands per c.mm.	Differential study.							Red cell studies.						Fragility tests with washed cells.		
						Poly. neut. per cent.	Poly. eosin. per cent.	Poly. baso. per cent.	Lymphocytes per cent.	Monocytes per cent.	Normoblasts per 100 W. B. C.	Reticulocytes per cent.	Macrocytosis.	Micrcocytois.	Polkiloeytois and poly- chromasia.	Stippling	Beginning hemolysis.	Complete hemolysis.	Normal control using washed cells.		
1931.																					
4/10	52	4.7	0.5	160	5.8	64.5	1	...	30	4.5	0	6	Mod.	Slight	Marked	+	0.40	0.20	0.46 to 0.30		
(a)																					
4/20	50	4.9	0.5	...	12.4	60	2	...	34	4	0										
(c)																					
4/24	50	4.5	0.5	180	11.2	54	5	1	38	2	0.5	11	Mod.	Slight	Marked	+	0.42	0.22	0.44 to 0.32		
(d)																					
4/24	51	4.6	0.5	280	32.0	43	4	1.5	47.5	4	0.5	10	Mod.	Slight	Marked	+	0.40	0.22	0.44 to 0.32		
(a)																					
4/28	50	4.7	0.5																		
(b)																					
5/17	40	3.9	0.5	...	9.0	57	43	...	0										
6/11	54	3.6	0.7	220	10.3	61	3	1	31	4	0.5	7	Marked	Slight	Marked	+					
9/26	60	5.2	0.5	150	9.1	63	4	0.5	29	3.5	0	10	Mod.	Slight	Marked	+					

REMARKS.—No sickle cells found in any of the smears; a, after an attack of abdominal pain; b, after a particularly severe attack of abdominal pain with cyanosis; c, before subcutaneous administration of 7 minims of adrenalin (1 to 1000); d, 15 minutes after administration of adrenalin.

the colored race. One of her sisters shows the sickling trait to a moderate degree.

The mother's parents and her forbears for generations were born and lived in Casabona, a town in Calabria, Italy. Here there has always been a strict social custom against intermarriage with other races. Negroes are unknown in this region; and in this connection it is interesting to note that the grandmother of the patient never saw a negro until she came to the United States at the age of about 25. The grandmother, who also shows sickle cells in her blood, was married in her native town, but gave birth to the patient's mother in the United States. She recalls her parents and grandparents on the paternal and maternal sides very well, and declares that they were all white in color, being even fairer in skin than the average Italian, and that they showed none of the facial characteristics of the negro race. By her appearance she certainly bears out this statement. Her husband, the grandfather of the patient, died several years ago of an unknown illness (see pedigree chart).

Past History. Negative.

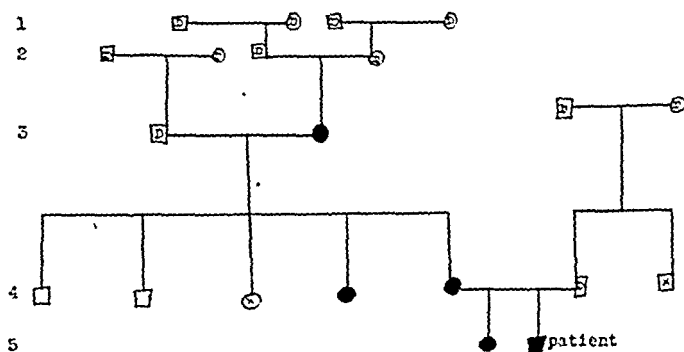


CHART I.—Family tree of patient, of which five generations can be recalled by its oldest living member and of which three generations show the sickling trait. Squares indicate males; circles, females. Black symbols indicate those with the sickling trait; symbols with cross inside represent negative examinations of blood for sickling; clear symbols indicate no examination of blood for sickling; symbols containing the letter *D* indicate dead persons. Numbers represent the generations.

Present Illness. Five years ago patient began to have attacks of severe abdominal pain, especially in the left upper quadrant, associated with inability to move the bowels but with no nausea or vomiting. The pain would persist for about 2 days, and then after a bowel movement it would disappear. These attacks recurred at intervals of 1 to 2 months at first, but later they increased in frequency, coming at intervals of 1 to 2 weeks. In the more recent attacks the pain was accompanied by fever. For the past year, weakness and profuse sweats have been noted.

Physical Examination. The patient showed no evidence of any negroid feature. There was a slight suggestion of a Mongoloid conformation of the eyes. The skin was a muddy yellowish color, and the mucous membranes were pale. The tonsils were small, buried, and apparently diseased. There was slight enlargement of the submaxillary and posterior cervical lymph nodes on each side; the other superficial lymph nodes were palpable but very small. There was a systolic blowing murmur over the precordium, transmitted to the left axilla. The blood pressure was 102/60. Abdominal examination revealed an enlarged spleen, reaching three fingers' breadth below the costal margin in the left nipple line. The liver edge was felt one

finger's breadth below the costal margin in the right nipple line. The extremities showed no ulcers or scars.

Laboratory Data. The blood Wassermann and Kahn reactions were negative. The uric acid was 4.2 mg., calcium 9.6 mg., phosphorus 4.8 mg., and cholesterol 184 mg., per 100 cc. of blood. The icterus index was 12. The van den Bergh test showed a positive direct delayed reaction and an indirect reaction of one unit. The urine was normal. Several urobilinogen and urobilin determinations ranged from 1200 to 2800 dilution units in 1000 cc. of urine and from 23,000 to 52,000 dilution units in the stools. The fragility tests and hematologic studies are reproduced in the accompanying table, and are later commented upon. Roentgenograms of the bones of the skull and of the extremities were negative.

Course. After 10 days in the hospital, the patient had an attack of severe upper abdominal pain, which was diffuse but worse in the left upper quadrant. At the same time he complained of severe headache and of pain in the joints of the right wrist and right knee. There were no objective arthritic signs. The sclerae which were previously clear now showed a slight icteric tinge. Four days after this attack, an adrenalin test was done, injecting 7 minims subcutaneously, a much larger dose than is ordinarily given. Within 1 minute the patient complained of epigastric pain, and had severe headache. On abdominal examination, the spleen was found to have receded from three fingers' breadth below the costal margin to such an extent that it was barely palpable beneath the costal margin. After 24 hours the spleen had returned to its original size.

During the following 4 weeks, the patient had about seven attacks of severe abdominal pain accompanied by severe headache and joint pains. Vomiting occurred when the headache was at its height; but not when abdominal pain alone was present. On three occasions a marked cyanotic spell occurred concomitantly with an attack, and it was necessary to use oxygen. On one such occasion a fatal termination seemed imminent. During the cyanotic attacks, his blood pressure was 132/80. Once the patient had a severe pain of stabbing character in the left side of his chest, aggravated by deep breathing. This was attributed to a splenic infarction. The temperature throughout ranged between 99° and 100.5° F, except for 2 days after one of the attacks of abdominal pain when it rose to 103°. The spleen remained unchanged in size during all the attacks.

The family of the patient refused to give permission for a splenectomy, and he was discharged May 26, 1931. Since his return home he has had frequent attacks of excruciating abdominal pain, usually in the left upper quadrant, but sometimes also in the right upper quadrant, accompanied by headache and joint pains, but with no cyanosis.

Hematologic Examination. The appended table shows the result of the various hematologic examinations. The important features to be noted are the low hemoglobin value with a relatively high erythrocyte count, giving a low color index, the mild degree of leukocytosis, the presence of normoblasts, reticulocytosis, macrocytosis, and the increased resistance of the red cells to hypotonic salt solution. It is worthy of note that no sickle cells were seen at any time in the stained smears, although there was a marked degree of poikilocytosis. It is also of interest to mention that, after one particularly severe attack of abdominal pain with headache and cyanosis, there was a significant increase in the degree of anemia. The urine was not tested for hemoglobin at this time, but the blood showed no gross evidence of hemolysis. The subcutaneous injection of adrenalin caused a prompt and marked contraction of the spleen, and produced a great increase in the number of leukocytes.

Sickling Phenomena. Wet preparations were made by placing a drop of blood on a very thin cover slip, inverting the latter on a glass slide, and

sealing the edges of the cover slip with vaseline. On immediate examination the preparations were entirely negative. After about 2 hours a few erythrocytes began to assume elongated, pointed forms, resembling oat or caraway seeds. In 24 hours, almost all of the red cells were transformed into typical sickle cells, as shown in the photomicrograph. On removing the cover slip the sickle cells immediately resumed their original round shape. If undisturbed the sickle cells kept their appearance for several days, and then began to become round again. In 7 to 10 days all the cells had returned to their original shape, and underwent no further changes except those of deterioration. It was also noted that occasionally a sealed wet preparation showed no sickling at all, although it was taken with the same technique and at the same time as positive preparations. Red cells washed four times with physiologic salt solution were likewise tested, and it was found that sickling took place to the same degree as in unwashed blood. Numerous attempts in this case to show the sickle cells on stained slides resulted in complete failure.

Because of the hereditary character of the sickling trait the blood of various members of the family of the patient were examined. The mother's blood showed a slight degree of sickling, about 3 to 5 per cent of the cells sickling in certain parts of the wet preparations. Her blood count was normal, the blood smears showed no abnormal red cells; the reticulocytes were less than 1 per cent; and the icterus index and the van den Bergh reaction were normal. The patient's sister, aged 12 years, had 1 per cent of sickle cells in her blood; her blood count, however, was normal, and stained smears showed no abnormal red cells. Her icterus index was 9; the van den Bergh reaction, direct, was negative and indirect, 1 unit; and the reticulocytes were less than 1 per cent. One of the maternal aunts of the patient showed from 10 to 20 per cent sickle cells in her blood. Two other maternal aunts and a paternal uncle had no sickle cells. Blood from the maternal uncles could not be obtained. The blood of the patient's maternal grandmother was found to have a few sickle cells, less than 0.5 per cent.

Comment. Thus the sickling trait has been definitely found in three generations of the above family; and in at least five generations it is known that the members have been of the white race. Nevertheless, the possibility cannot be absolutely ruled out that in a previous remote generation there might have been a negro ancestor with sickle cells in the blood and that the sickling trait, known to be transmitted as a dominant Mendelian character, might have been handed down thereby to white descendants with no external trace of any of the negro features. This possibility must receive serious consideration, for the weight of evidence at the present time seems to indicate the negro origin of sickling. That other races might be subject to the sickling trait has been suggested by Moore,¹⁶ who found a high incidence of bone changes, similar to those that occur in some cases of sickle-cell anemia, in the skulls of the ancient Mayan Indians. Cooley and Lee¹⁴ suggested that the sickling trait be looked for in those of the Mediterranean races presenting the picture of an atypical hemolytic icterus. Previously these authors¹⁷ had described a peculiar form of atypical hemolytic icterus with bone changes in 7 children, 5 of whom were of Mediterranean racial origin. The entire subject is thus of unusual ethnologic interest.

Recognition of sickle-cell anemia in white persons may be facili-

tated if its resemblance to congenital hemolytic icterus is borne in mind. All cases of atypical hemolytic icterus, such as those with an absence of increased fragility of the erythrocytes or those with a macrocytosis instead of a microcytosis, deserve an examination of the blood for sickle cells. Since stained smears may fail to show such cells, it is necessary to make several sealed wet preparations, and to watch these for at least 24 hours before deciding on the presence or absence of sickling.

It is to be expected that in the future more cases of sickle-cell anemia in white persons will be discovered. The reasons for this statement are as follows: First, since attention has been called to the occurrence of the sickling trait in the white race, more frequent examinations of the blood for sickle cells will be made, especially in those patients presenting the syndrome of an atypical hemolytic icterus. Thus, more cases of the type described in this paper may be discovered. Second, since it is known that the sickling trait is a dominant character in its hereditary transmission and since interbreeding between the colored and the white races is more or less constantly taking place in many regions, including this country, we may in future generations expect the presence of this peculiar blood trait in an increasing number of apparently white descendants. Because of the tendency to deny such descent by those who are free of all negro features, no history will be obtained of such racial origin in affected individuals, thereby increasing the number of apparently pure white cases of sickle-cell anemia.

Summary. 1. A review of the literature of sickle-cell anemia in the white race reveals only one previous case where no evidence of a possible admixture of negro blood can be discovered. A second case is cited where the data are incomplete for such a conclusion.

2. A third case is here reported in a family where three generations show the sickling trait and at least five generations are known to be of the white race from a region where negroes are practically unknown.

3. The ethnologic and clinical feature of the subject are discussed.

4. Reasons are given for expecting an increase in the number of cases of sickle-cell anemia in the white race.

BIBLIOGRAPHY.

1. Herrick, J. B.: *Arch. Int. Med.*, 1910, **6**, 517.
2. Sydenstricker, V. P.: *South. Med. J.*, 1924, **17**, 177; *J. Am. Med. Assn.*, 1924, **83**, 12; *Med. Clin. No. Am.*, 1929, **12**, 1451.
3. Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W.: *Am. J. Dis. Child.*, 1923, **26**, 132.
4. Huck, J. A.: *Bull. Johns Hopkins Hosp.*, 1923, **34**, 335.
5. Graham, G. S., and McCarty, S. H.: *South. Med. J.*, 1930, **23**, 598.
6. Steinberg, B.: *Arch. Path.*, 1930, **9**, 876.
7. Castana, V.: *La Pediatria*, 1925, **33**, 431.
8. Schilling, V.: *The Blood Picture*—translated by Gradwohl, The C. V. Mosby Company, St. Louis, 1929, page 101; also plate I, Fig. 43, and plate III, Figs. 6 and 8.

9. Lambin, P., and Leto, A.: *Rev. belge d. sci. m d.*, 1930, 2, 246.
10. Archibald, R. G.: *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1926, 19, 389.
11. Stewart, W. B.: *Am. J. Dis. Child.*, 1927, 34, 72.
12. Lawrence, J. S.: *J. Clin. Invest.*, 1927, 5, 31.
13. Lawrence, J. S.: *AM J. MED. SCI.*, 1931, 181, 240.
14. Cooley, T. B., and Lee, Pearl: *Am. J. Dis. Child.*, 1929, 38, 103.
15. Sight, W. P., and Simon, S. D.: *J. Med.*, 1931, 12, 177.
16. Moore, S.: *J. Missouri Med. Assn.*, 1929, 26, 561.
17. Cooley, T. B., Witwer, E. R., and Lee, P.: *Am. J. Dis. Child.*, 1927, 34, 347.

THE BASAL METABOLISM IN PERNICIOUS ANEMIA AND SUB-ACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

By M. M. SUZMAN, M.D., M.R.C.P. (LONDON),

MEDICAL RESEARCH FELLOW, ROCKEFELLER FOUNDATION, AND RESEARCH FELLOW IN MEDICINE, MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL, BOSTON.

(From the Medical Services and Metabolism Laboratory of the Massachusetts General Hospital, Boston.)

THIS investigation is part of an attempt to ascertain more about the nature of subacute combined degeneration of the cord and its relation to pernicious anemia by a study of systems other than that of the blood, nervous system and alimentary tract.

The observation, first pointed out to me by Dr. Wyman Richardson, that a low basal metabolic rate not infrequently exists in pernicious anemia, seemed of especial importance, since, from the various records in the literature of the basal metabolic rate in this disease, one was led to believe that the rate was more often either elevated or within normal limits than decreased. Therefore, during the course of an investigation concerning the effects of liver therapy in a large series of cases of pernicious anemia with and without subacute combined degeneration, opportunity was taken of noting the basal metabolic rate in a considerable number of cases. In addition, metabolic readings previously recorded in the Metabolism Laboratory of the Massachusetts General Hospital on patients with these diseases were incorporated into this series. Thus, estimations of the B.M.R. were obtained in 130 cases of pernicious anemia, and grouped according to whether or not subacute combined degeneration of the spinal cord was present. Comparative analyses of the metabolic rates in these two groups, and a discussion of the possible significance of the difference observed, together with a short review of the literature, form the subject of this paper.

In this series of 130 cases, the basal metabolic rates of 36 patients, of whom 12 had spinal cord involvement, were determined before liver treatment was instituted. However, since no significant alterations in the ultimate results were found on separating the basal

metabolic rates of the liver-treated cases from those of patients who were not so treated, it was considered that all the cases could be analyzed together.

In the diagnosis of subacute combined degeneration of the cord, the criteria followed were identical with those used elsewhere^{1,2} and which may be reiterated here. This group includes only those cases of pernicious anemia which have shown definite signs of involvement of either the posterior or lateral columns of the spinal cord, or of both these columns. Incoördination and ataxia from loss of muscle and joint sensibility, and in addition loss of vibration sense, are the signs which have been regarded as evidence of involvement of the posterior columns. The "extensor" type of plantar reflex (Babinski's sign), with or without exaggeration of the deep reflexes, and patellar or ankle clonus, are the signs used to indicate degeneration of the pyramidal fibers of the lateral columns. Although it is realized that in pernicious anemia numbness and tingling of the extremities are probably indicative of involvement of the peripheral nerves or even possibly of the spinal cord, the presence of such symptoms alone has not been regarded as sufficient to warrant a diagnosis of subacute combined degeneration. Such cases, therefore, were included in the uncomplicated pernicious anemia group. However, in order to ascertain into which group the basal metabolic rate of these cases would tend to fall, they were further segregated from the general pernicious anemia group and plotted. It will be seen from Chart I that these cases of pernicious anemia with paresthesia alone and those without these symptoms are similarly distributed, contrasting markedly with those diagnosed as pernicious anemia with subacute combined degeneration. According to the above diagnostic criteria, this series of 130 cases consists of 65 instances of pernicious anemia with, and a similar number without, subacute combined degeneration.

All the determinations were carried out on the Benedict-Roth basal metabolism apparatus. When two or more readings were obtained on the same patient the lowest was always used, since by so doing the error entailed is least. In the few instances in which fever was present during the test, the reading was corrected according to the Du Bois formula of 7.2 per cent reduction per 1° F. All cases presenting either thyrotoxicosis or myxedema were excluded from this series, the coexistence of the latter condition and pernicious anemia having already been reported from this clinic.³

From Table 1 it will be seen that of the 65 cases of pernicious anemia without spinal cord involvement, 41.5 per cent have a basal metabolic rate above +10 per cent and there is none below -9 per cent, whereas of the 65 cases of pernicious anemia with subacute combined degeneration only 3 per cent have a rate above +10 per cent and there are 43.1 per cent with a basal metabolism of -10 per cent or less.

TABLE 1.—DISTRIBUTION TABLE OF THE BASAL METABOLISM IN PERNICIOUS ANEMIA, WITH AND WITHOUT SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

Basal metabolic rate.	Pernicious anemia without spinal cord involvement (65 cases), per cent.	Pernicious anemia with spinal cord involvement (65 cases), per cent.
Above +20	18.5	0.0
+11 to +20	23.0	3.0
+1 to +10	40.0	18.5
0 to -9	18.5	35.4
-10 to -19	0.0	32.3
-20 and under	0.0	10.8

The tendency for elevated metabolic rates to be found in pernicious anemia and other forms of anemia has been pointed out by several investigators, *e.g.*, Magnus-Levy,⁴ Rolly⁵ and Meyer and DuBois.⁶ Boothby and Sandiford⁷ in a group of 19 cases of pernicious and splenic anemia found that 15.9 per cent had a basal metabolism below -10 per cent and 21.1 per cent above +10 per cent. In a later publication,⁸ bearing on 36 cases of pernicious and splenic anemia, only 6 per cent had rates below -10 per cent whereas in 41 per cent the basal metabolism was above +10 per cent. These figures are very similar to those obtained in the present series of cases of pernicious anemia without spinal cord involvement. Tompkins, Brittingham and Drinker,⁹ in a series of 12 cases of pernicious anemia, pointed out that the recent more acute cases gave an elevated metabolic rate, whereas a diminished rate was the rule in the long-standing chronic cases. It would have been interesting to know whether or not neurologic involvement was a feature in these chronic cases with low metabolic rates. These investigators also made the important observation that in all cases the metabolic rate fell when the red blood cell level increased as a result of blood transfusion. Coincident with the fall in the metabolic rate and the increase in the numbers of red blood cells, there was a diminution in the pulse and respiration rates and a fall in temperature. The tendency to elevation of the basal metabolic rate in pernicious anemia and its diminution during remission has also been noted by other investigators.^{10,11,12} Alt¹² made a study of 5 cases of pernicious anemia treated with liver extract, noting the basal metabolism at intervals throughout the remissions. He observed that the metabolic rate, normal at first, rose during the reticulocyte crisis, fell rapidly during the increase of red blood cells and finally returned to within normal limits. The diminution in basal metabolism during the formation of new red blood cells was accounted for, according to this writer, by the fact that when ingested protein is deposited as new tissue, its amino acids cease to exert a specific dynamic action on metabolism. Decrease in pulse and respiration rate, and in the temperature, and again in body weight were also considered as contributory causes. Richards and Strauss¹¹ pointed

out that in anemia, in addition to a tendency for the basal metabolic rate to be elevated, there is an increase of the cardiac output and of the percentage utilization of oxygen by the tissues. These two latter adjustments were considered the means by which the burden of the diminished oxygen capacity on the circulation is borne, and, together with the elevated basal metabolism, diminished coincident with the remission of the anemia. That there is a tendency for the basal metabolism to diminish coincident with amelioration of the anemia is confirmed by several instances in the present series of cases, in which metabolic rates were determined in the same case at different levels of the red blood cell count.

Since it is evident that the basal metabolism in any given case depends to a large extent on the red blood cell level, and since there is a tendency for cases of pernicious anemia with neurologic involvement to come under observation with a lesser degree of anemia than those without such involvement, it was considered possible that the marked disparity in the metabolism of these two groups may be accounted for by differences in the red blood cell counts. In order to ascertain to what extent this may have been the case, the metabolic readings in each group were plotted against their respective red cell counts (Chart I). Moreover, it was considered that this procedure would tend also to obviate any discrepancies which may arise due to the fact that almost all the red blood cell counts of the cases not treated with liver were less than 3 millions per c.mm., in contrast to those of the liver-treated patients, in whom there was a large proportion of red blood cell counts above this level.

From Chart I, it is evident that at any given red blood cell level, there is a distinct tendency for the basal metabolism in pernicious anemia with subacute combined degeneration to be substantially lower than in pernicious anemia without involvement of the central nervous system. It is evident, therefore, that the difference between the two groups is more than can be accounted for by differences in the red blood cell levels.

Furthermore, analyzed statistically,* it is found that the ratio of the difference between the mean basal metabolism of each group (20.2), to the probable error of the difference between the means (1.17) is 17. From this it may be concluded that the odds against the occurrence of such a difference as found between the two means is so great as to make it practically certain that the basal metabolism is lower in the group of cases with spinal cord involvement. It is of interest that Williams¹³ has observed diminished basal metabolic rates in several cases of subacute combined degeneration of the cord.

The tendency for a low metabolic rate to be found in pernicious anemia with subacute combined degeneration may conceivably be explained on the basis of the neuromuscular disability and the

* Kindly carried out by Dr. I. M. Rabinowitz of Montreal General Hospital.

curtailing of general body activities, thereby slowing up oxidation processes. In order to ascertain to what extent this hypothesis may be true, the basal metabolic rates of the patients with subacute combined degeneration were further analyzed according to the degrees of disability. For this purpose the cases were separated into certain convenient, though arbitrary, groups, as follows: (1) those who were bedridden, (2) those who required crutches or aid in order to walk, (3) those who could get about with the help of a cane, (4) those in whom there was slight unsteadiness on walking, and (5) those who were able to walk "essentially" normally.

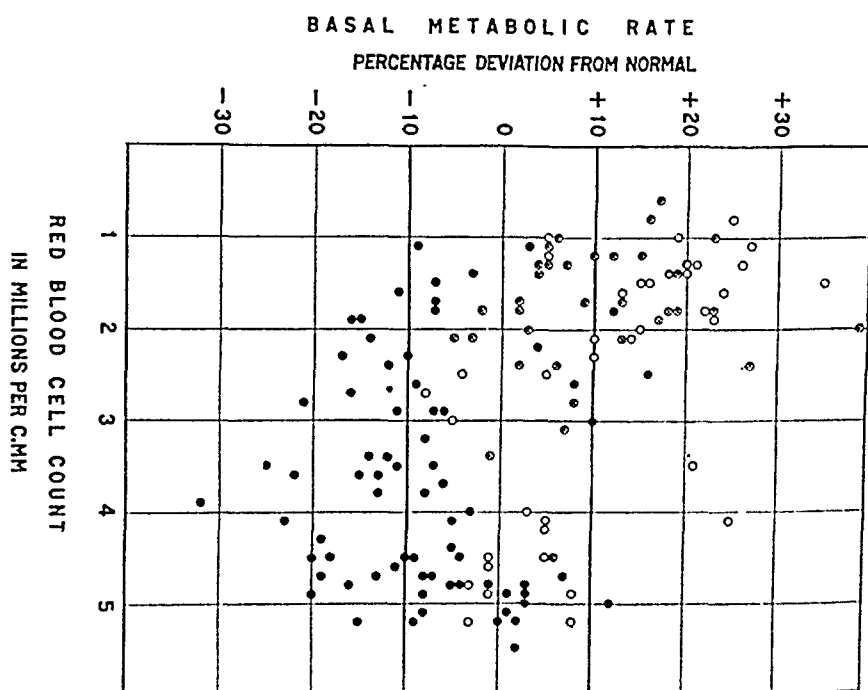


CHART I.—The relation of the basal metabolism to the red blood cell level in pernicious anemia, with and without subacute combined degeneration of the spinal cord.

- | | | |
|--|---|---|
| ○, Denotes pernicious anemia without paresthesia | } | 73 basal metabolic readings on 65 patients. |
| ⊗, Denotes pernicious anemia with paresthesia only | | |
| ●, Denotes pernicious anemia with subacute combined degeneration | | 71 basal metabolic readings on 65 patients. |

On comparing the basal metabolism of these five groups, it was found that there was no greater tendency for bedridden patients to have low basal metabolism than for those with only slight unsteadiness on walking, or for those with intermediate grades of disability. It is noteworthy, however, that in all the 11 cases in which liver treatment had brought about almost complete relief from neuromuscular disability, the basal metabolic rates were within normal

limits, and this in spite of the high level of red blood cell counts in this group (see Table 2). Unfortunately, no data are available concerning the basal metabolism in these 11 patients before liver treatment was commenced, or before their difficulty in walking had completely disappeared.

TABLE 2.—THE BASAL METABOLISM IN 65 CASES OF PERNICIOUS ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD, GROUPED ACCORDING TO THE DEGREE OF DISABILITY.

Degree of disability.	No. of cases.	Average B.M.R., per cent.
Bedridden	18	-10.0
Crutches	8	- 6.4
Cane	12	- 9.0
Slight unsteadiness	16	- 9.1
None	11	- 2.3
Totals	65	- 7.9

On account of the tendency for the basal metabolism to become elevated when the red blood cell level is diminished, it must be realized that the average basal metabolic rates of each of the above groups are not strictly comparable. In order to obviate this discrepancy, all the basal metabolic rates determined in patients with red blood cell counts below 3.5 millions per c.mm. were discarded. The remaining 39 cases were compared and the results are given in Table 3. It may be seen that this process of elimination brought about a slightly lower average basal metabolic rate for each group, the diminution being greatest in the bedridden group, and negligible in individuals with no disability. Although the number of cases available for consideration is thus considerably reduced, giving the results, as a whole, perhaps somewhat less significance, elimination of the low red blood cell counts ensures, at least, that all the basal metabolic rates are comparable.

TABLE 3.—THE BASAL METABOLISM IN 39 CASES OF PERNICIOUS ANEMIA WITH SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD WITH RED BLOOD CELL COUNTS OF 3.5 MILLIONS PER C.MM. AND OVER, GROUPED ACCORDING TO THE DEGREE OF DISABILITY.

Degree of disability.	No. of cases.	Average B.M.R., per cent.
Bedridden	8	-14.8
Crutches	3	- 8.0
Cane	9	- 9.8
Slight unsteadiness	10	-11.2
None	9	- 2.4
Totals	39	- 9.3

From the above data, it seems that the finding of a marked difference between the average basal metabolic rates of the patients with and of those without neuromuscular disability is not incompatible with the hypothesis that disability is the factor responsible for the tendency for a diminished oxygen consumption in subacute combined degeneration. However, it is difficult to conceive why

the patients with but slight unsteadiness on walking should also tend to have a diminished basal metabolism. Moreover, if the hypothesis that disability may be the cause of this diminution were true, one would expect similar low readings in other crippling nervous disorders, such as tabes dorsalis, disseminated sclerosis, transverse myelitis, and the like. Although the data on this subject are comparatively scanty, it appears that in such conditions the oxygen consumption is usually within the normal limits. Of 20 cases of sclerosis of the central nervous system and tabes dorsalis, reported by Boothby and Sandiford,⁷ 90 per cent had a basal metabolism between -10 per cent and $+10$ per cent, the remaining 10 per cent being between $+11$ per cent and $+15$ per cent. Grafe,¹⁴ while studying the basal metabolism in such neurologic conditions as encephalitis lethargica, multiple sclerosis, traumatic transverse myelitis, etc., noted that the metabolism was within normal limits, regardless of whether the paralyzes were of the spastic or of the flaccid type. It is of interest to note that this writer pointed out that in neurologic conditions, hypertonicity, spasm, and even tremor of the muscles do not tend to increase the basal oxygen consumption, and believed that muscles under these conditions are able to work more economically than in the case of voluntary contractions.

Although it is not unlikely that the tendency for a low basal metabolism to be a feature in subacute combined degeneration may be explained on the basis of neuromuscular disability, the evidence in support of such an hypothesis is not conclusive, and it is possible that some other factor may be responsible.

Several of the patients with diminished basal metabolism exhibited definite, though usually mild, hypothyroid symptoms, but in no case was true myxedema present. Such symptoms as dry skin, absence of perspiration, intolerance to cold and a poor memory were commonly noted. It is noteworthy that a low basal metabolic rate was not always accompanied by symptoms which occur with hypothyroidism.

Relief from such symptoms, and a return of the diminished basal metabolism to normal, were readily brought about by the administration of thyroid extract, the usually daily dose being 3 grains of Armour's preparation, but in no instance could improvement in the neurologic condition be attributed to this drug. The administration of liver, while resulting usually in marked neurologic benefit, did not appear to have any appreciable effect on the hypothyroid symptoms.

Summary. 1. The basal metabolic rates of 65 cases of pernicious anemia without, and of 65 cases with, subacute combined degeneration of the spinal cord have been studied.

2. In pernicious anemia without spinal cord degeneration, the basal metabolism tends to be either normal or elevated (41.5 per cent of the cases had a B.M.R. of over $+10$ per cent), but in per-

pernicious anemia with subacute combined degeneration there is a distinct tendency for diminution to occur (43.1 per cent had a B.M.R. below -9 per cent).

3. The basal metabolism is influenced by the level of the red blood cells. In the cases with subacute combined degeneration the red blood cell counts were, on the whole, higher than in the group of patients with uncomplicated pernicious anemia. The data show, however, that the tendency for diminution of the B.M.R. to occur in patients with subacute combined degeneration of the cord exists at all levels of the red blood cells. Therefore the red blood cell level cannot be regarded as the responsible factor.

4. Consideration is given to the possibility that the diminished basal metabolism in cases with subacute combined degeneration may be the result of neuromuscular disability.

5. The symptomatology and the effects of thyroid administration in the cases with low basal metabolism are presented.

NOTE.—I am grateful to Dr. J. H. Means for permission to use the cases in the Medical Services and Outpatient Departments of the Massachusetts General Hospital, and for facilities extended in the Metabolism Laboratory. I am also indebted to Dr. J. Lerman and the Staff of the Metabolism Laboratory for their kind coöperation, and to Dr. G. R. Minot for his kindly help and criticism.

REFERENCES.

1. Ungley, C. C., and Suzman, M. M.: *Brain*, 1929, **52**, 271.
2. Suzman, M. M.: *Trans. Am. Neurol. Assn.*, 1931. (In press.)
3. Means, J. H., Lerman, J., and Castle, W. B.: *New Eng. J. Med.*, 1931, **204**, 243.
4. Magnus-Levy, A.: *Ztschr. f. klin. Med.*, 1906, **60**, 179.
5. Rolly, F.: *Deutsch. Arch. f. klin. Med.*, 1914, **114**, 605.
6. Meyer, A. L., and Du Bois, E. F.: *Arch. Int. Med.*, 1916, **17**, 965.
7. Boothby, W. M., and Sandiford, I.: *J. Biol. Chem.*, 1922, **54**, 783.
8. Boothby, W. M., and Sandiford, I.: *Phys. Rev.*, 1924, **4**, 69.
9. Tompkins, E. H., Brittingham, H. H., and Drinker, C. K.: *Arch. Int. Med.*, 1919, **23**, 441.
10. Grassheim, K.: *Ztschr. f. klin. Med.*, 1929, **111**, 601.
11. Richards, D. W., and Strauss, M. L.: *J. Clin. Invest.*, 1928, **5**, 161.
12. Alt, H. L.: *Arch. Int. Med.*, 1929, **43**, 488.
13. Williams, J. P.: Personal Communication; also *Bull. McGuire Clinic and St. Luke's Hospital*, 1929, **1**, 133.
14. Grafe, E.: *Deutsch. Arch. f. klin. Med.*, 1922, **139**, 155.

THE DIFFERENTIATION OF LYMPHATIC LEUKEMIA FROM AGRANULOCYTIC ANGINA.

By H. A. ROTHROCK, JR., M.D.,

PATHOLOGIST TO THE ST. LUKES HOSPITAL,
BETHLEHEM, PA.

(From the William Henry Chandler Pathological Laboratory, St. Lukes Hospital.)

MANY cases of agranulocytic angina have been reported in the literature since this was given importance as a supposedly clinical entity by Schultz¹ in 1922 and by Kastlin² in this country in 1927.

That the condition had been reported previously to these papers has been shown by the reports of Brown³ and Turk.⁴ The wave of enthusiasm that follows the description of any new and interesting disease has caused it to be searched for more carefully and found more often than it would have been otherwise. One cannot but wonder if the enthusiasm of the searchers does not at times carry them beyond the warranted conclusions, particularly in those cases without autopsy. Atypical states of well-known though uncommon conditions are reported as one of the newer clinical entities. In a review of the numerous cases of agranulocytic angina recently reported, there have appeared not a few that have made the writer believe that the reporter's interest in the new condition has clouded the clinical and laboratory findings that really point to a supposedly less interesting diagnosis. With the realization that this has probably taken place in some interpretations, the following case is reported to impress the fact that, though new diseases of the utmost interest may be discovered, the old diseases must be given due recognition; and further, that any conclusion drawn from a case that has not had a postmortem examination must be made very conservatively. For even when there is an autopsy to complete the study of the case, the diagnosis and the pathologic processes involved are often still clouded by our own lack of knowledge, especially in diseases that primarily involve the hemolytopoietic system.

Case Report. E. L., a white male, married, aged 32 years, was admitted to the hospital on the service of Dr. F. J. Dever on December 22, 1931. The patient's condition was too critical to permit taking a history directly from him and the following history was obtained from his wife. About 6 weeks previous to admission, the patient returned from work feeling tired and weak. He went to bed early, but was awakened from sleep by an attack of acute abdominal pain. His wife stated that his abdomen was much distended. He received medical attention but no definite diagnosis was made. From then on he complained of general weakness. Three weeks before admission he began to notice a bleeding from his gums, a constant "oozing," which medical treatment did not control. Refusing to go to a hospital, he became progressively weaker, but was not confined to bed. Five days before admission he began to complain of a sore throat, which three days later had progressed to a peritonsillar abscess which was lanced with some relief. He became rapidly worse and was admitted to the hospital in a semistuporous condition. His wife was unable to give any noteworthy information about his past medical history.

Physical Examination (Dr. H. W. Wright). The patient is a fairly well nourished adult male who appears to be desperately ill and very anemic. He continually spits up bloody material and breaths with great difficulty. Scalp is negative. Eyes: pupils react poorly; equal in size. The ears are negative. Mouth: there is a constant bloody oozing from the gums. The throat is extremely red, swollen and ulcerated with purpuric spots on the roof of the mouth. Neck: the lymph nodes are enlarged. The lungs are negative. Heart: the rate is rapid but regular; the sounds are of poor quality. The abdomen is negative; spleen not palpable. The extremities are negative. Skin: there are ecchymotic spots over the chest and arms.

FIG. 1.

FIG. 2.

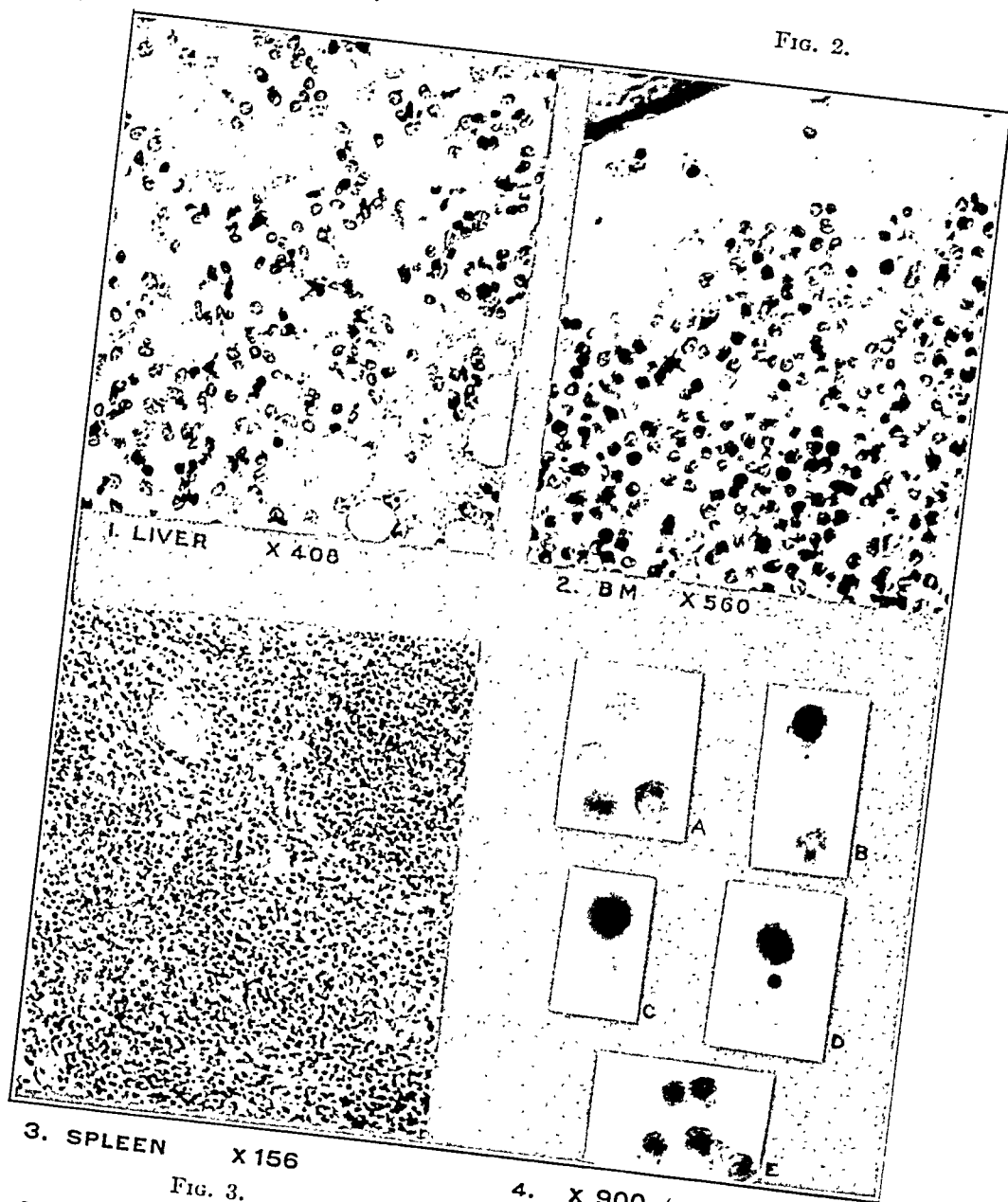


FIG. 3.

4. X 900 (RETOUCHED)
FIG. 4.

FIG. 1.—Liver, showing infiltration of lymphocytes and fatty infiltration of liver cells. 408 X.
FIG. 2.—Bone marrow, showing widespread lymphocytic infiltration. 560 X.
FIG. 3.—Spleen. Central artery with loss of normal structure of surrounding Malpighian body. 156 X.
FIG. 4.—Blood smear (peroxidase stain). Retouched photographs. A, two lower cells are lymphocytes; two upper cells are erythrocytes; B, lower cell is a neutrophil; C and D, upper cells are lymphocytes; E, 4 lymphocytes. Peroxidase granules do not stain. 900 X.

Eye grounds (Dr. G. E. deSchweinitz) show a widespread retinitis with every type of hemorrhage, old and fresh. The optic disks are pale. There is no optic neuritis or choking of the disks. Where visible, the arteries and veins appear normal in size and color. There are some areas where there is a red rim and a white center which is suggestive of lymphatic leukemia.

Progress and Treatment. The patient received general supportive treatment, local antiseptics to the throat, and a blood transfusion. His temperature remained between 104° and 105° F., his pulse around 135 and his respirations remained around 35. He grew progressively worse and died 3 days after admission.

Laboratory Findings. Urine: faint trace of albumin with an occasional hyaline cast. Coagulation time, 4 minutes. Blood urea nitrogen, 15 mg. per 100 cc. Throat culture: staphylococci with an occasional streptococcus. Blood culture, no growth. Blood counts are recorded in the following table:

Date.	December 22.	December 23 (9 A.M.).	December 23 (3 P.M.).	December 24.
Red cells (millions)	1.3	1.4	1.3
Hemoglobin (gm. per 100 cc.)	3.4	4.7	2.1
Leukocytes	19,000	18,000	7,700	6,700
Neutrophils:				
Number	2,100	700	380	400
Per cent	11	4	5	6
Lymphocytes:				
Number	17,000	17,000	6,600	6,100
Per cent	89	95	85	91
Monocytes:				
Number	770	134
Per cent	10	2
Reticulocytes (per cent)	1	

The differential smear showed the white cells to be made up mostly of mature lymphocytes. The percentage of monocytes, which in one count reached 10 per cent of the leukocytes, confirms the low percentage of young polymorphonuclear forms, for young forms if present would probably have been classified with these large mononuclear cells. The peroxidase stain was negative on all granulocytic cells making the identification of myelocytes inaccurate.

Autopsy (limited to the abdomen). General examination showed a pale, white, fairly well-nourished male with numerous ecchymotic spots of the skin, most pronounced on the extremities. Lymph nodes slightly enlarged. The liver (2500 gm.) is very pale, the surface smooth and regular, the cut surface not showing any masses or irregularities. The gall bladder does not show any gross abnormalities. The pancreas appears normal. The spleen (400 gm.) is pale and soft, the surface smooth and regular; the cut surface rather pale, grayish and homogeneous. The follicles cannot be seen. The kidneys are both enlarged, very pale and flabby. Both kidneys contain several hematmata, 0.5 to 3 cm. in diameter, some of which protrude into the pelvis. The cortex and medulla are poorly defined. The gastrointestinal tract shows an occasional petechial hemorrhage. The mesenteric and omental lymph nodes are not increased in size.

It was not until the microscopic sections were examined that a definite diagnosis could be made. These all showed the typical changes found in lymphatic leukemia. The lymphocytic infiltrations were of course not as widespread as would be found in a case of longer standing.

Pathologic Histology (Abstract). The spleen showed lymphoid hyperplasia with a loss of normal architecture. In areas vestiges of Malpighian corpuscles could be found around the arteries, but these appeared to melt into the surrounding tissue without any definite boundary. The bulk of

the tissue appeared to be made up almost entirely of adult lymphocytes. There was very little blood in the organ; in some areas there were scattered blood cells in the venous sinuses. Polymorphonuclear leukocytes could only be found after prolonged search. The liver showed fatty infiltration with lymphocytes scattered between the liver cells and massive collections around the portal canals. A mesenteric lymph node showed a uniform hyperplasia of lymphocytes with a loss of normal structure and some infiltration into the surrounding fat. The bone marrow showed an over-running of the tissue with lymphocytes. Young forms of the red cell and granulocytic series were very difficult to find. This explained the lack of ability of these cells to take the peroxidase stain, for the bone marrow was nearly exhausted from the infiltration of the lymphocytes. The kidneys showed the borders of the hematomata to be made up of masses of lymphocytes which infiltrated into the surrounding tissue, making this tissue resemble a lymph node with here and there a renal tubule or glomerulus. The rest of the kidney showed parenchymatous degenerative changes.

Discussion. In reviewing the clinical aspects of this case, we have a young man admitted to the hospital in a critical condition. His fever, pulse, and the condition of his mouth and throat show him to be suffering from a very acute process at the time of admission. Petechial hemorrhages, however, lose a great deal of value in differential diagnosis in acute conditions like this. The whole process appears to have taken place within 6 weeks, while the more severe symptoms are limited to 3 weeks with the first complaint of sore throat 5 days before admission. His clinical picture is much like agranulocytic angina as described by Schultz¹ and Kastlin.² Naturally our interest immediately centered around the blood picture, especially the white and differential counts. The white count at the time of admission was 19,000 with the differential showing 11 per cent polymorphonuclears (total, 2100) and 89 per cent lymphocytes (total, 17,000) (an absolute lymphocytosis and an absolute neutropenia). This and the following counts bring out the importance of reporting the cells in actual numbers and doing away entirely with the often misleading and usually useless terms of relative lymphocytosis, relative lymphopenia, etc. The lymphocytes in this count appeared to be mature in form; the polymorphonuclears did not show a shift to the left. The count made the following day showed the neutrophils to have dropped to 700 while the lymphocytes had not shown any appreciable change. The patient was clinically worse than on admission. The afternoon of the second day in the hospital the lymphocytes had decreased to 7700 and the neutrophils to 380 per c.mm. At this time a peroxidase stain was made. It was found that only an occasional neutrophil would show the peroxidase granules and only one granular myelocyte was found after a prolonged search. The cells of both the lymphocytic and granulocytic series still appeared to be mature cells. The unsuccessful peroxidase stain suggests that these cells were being produced by a diseased, inefficient bone marrow. At this time the differential diagnosis lay between an acute lymphatic leukemia and

an agranulocytic angina. If a case of leukemia, the short duration and severe character would point to an acute form where we would have expected the count to be higher with the presence of many immature forms. It is true that the retinal hemorrhages resembled those of a lymphatic leukemia; but these and petechiæ are also found in other blood disturbances. The patient had a neutropenia on admission and up to his death the lymphocytes were dropping in number, which is characteristic of a typical agranulocytosis. At the time of death the patient was diagnosed as a case of agranulocytic angina. If agranulocytic angina is a clinical entity this diagnosis was in error, but if agranulocytic angina is a clinical syndrome the diagnosis was correct, be the cause of this syndrome what it may.

That agranulocytic angina is a clinical entity appears unlikely from the diversified conditions and blood pictures that are reported as occurring with, and probably causing this condition. This syndrome in a modified form, more chronic; has been associated with the administration of drugs derived from benzene (Farley⁵). These cases are not acute and quite often recover. I have seen 3 typical cases, in all of which the blood count went to below 1000. These 3 cases were all fatal. The interesting point of one case was that it developed in an elderly diabetic who had been under close supervision for over a month and at the time of the acute onset was well standardized. Conner *et al.*⁶ have reported a series of cases of agranulocytosis in which there appears to be a diversity of etiologic factors and severity of attack. Most investigators report an aplasia of the granulocytic series in the bone marrow, however Fitz-Hugh and Krumbhaar⁷ have recently reported a case in which they show that though the patient had a profound leukopenia in the peripheral blood, the bone marrow showed an increase in the forerunners of the granulocytic series, suggesting a maturation defect. It would seem that the conclusion to be drawn from all this diversity of opinion and clinical and postmortem findings is that agranulocytic angina cannot as yet be considered as a clinical entity. It certainly should not be considered a clinical entity until the cases such as the one here reported and other types of neutropenia of known origin have been weeded out. It would further appear that, when a true case of agranulocytosis is found, the altered blood picture is simply a decrease in the granulocytic cells of the blood stream, from either increased destruction or decreased formation, or both. When no definite cause for this condition can be uncovered, it is permissible to diagnose the case as agranulocytic angina; but before this is done a primary cause must be carefully searched for, with the burden of proof resting on the person making the diagnosis of agranulocytic angina.

Summary. 1. Cases other than those that should be classified as agranulocytic angina are not infrequently appearing in the literature under this heading.

2. A case of apparent agranulocytosis in which autopsy showed the cause to be a lymphatic leukemia is reported. Though clinically acute, this case was hematologically a chronic type of leukemia.

3. In the light of this and of cases in the literature, agranulocytic angina is regarded as a syndrome rather than a clinical entity.

REFERENCES.

1. Schultz, W.: Ueber eigenartige Halserkrankungen, *Deutsch. med. Wchnschr.*, 1922, 48, 1495.
2. Kastlin, G. J.: Agranulocytic Angina, *Am. J. Med. Sci.*, 1927, 173, 799.
3. Brown, P. K.: A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leukopenia, *Am. Med.*, 1902, 3, 649.
4. Turk, W.: Septische Erkrankungen bei Verkümmerng des Granulozyten-systems, *Wien. klin. Wchnschr.*, 1907, 20, 157.
5. Farley, D. L.: Depressed Bone Marrow Functions from the Arsphenamines (Including a Type of So-called Agranulocytosis), *Am. J. Med. Sci.*, 1930, 179, 214.
6. Conner, H. M., Margolis, H. M., Birkeland, I. W., and Sharpe, J. E.: Agranulocytosis and Hypogranulocytosis, *Arch. Int. Med.*, 1932, 49, 123.
7. Fitz-Hugh, T. Jr., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, *Am. J. Med. Sci.*, 1932, 183, 104.

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES.

V. THE COEXISTENCE OF TUBERCULOSIS WITH HODGKIN'S DISEASE AND OTHER FORMS OF MALIGNANT LYMPHOMA.

BY FREDERIC PARKER, JR., M.D.,

ASSISTANT PATHOLOGIST, BOSTON CITY HOSPITAL; ASSISTANT PROFESSOR OF PATHOLOGY,
HARVARD MEDICAL SCHOOL,

HENRY JACKSON, JR., M.D.,

JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL; ASSOCIATE PHYSICIAN, COLLIS
P. HUNTINGTON MEMORIAL HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE,
HARVARD MEDICAL SCHOOL,

AND

JAMES M. BETHEA, M.D., AND FRANK OTIS, M.D.,

BOSTON, MASS.

(From the Pathological Laboratory and the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Collis P. Huntington Memorial Hospital and the Department of Medicine, Harvard University.)

Ever since Sternberg, in 1898,¹ called attention to the frequent association of tuberculosis and Hodgkin's disease, speculation has been rife as to the etiologic rôle of the tubercle bacillus in this latter disease. An enormous amount of experimental work has been done in an attempt to settle the question, but differences of opinion still exist among competent pathologists.

Several lines of attack may be followed in the investigation of

the problem. The results of animal injection, bacteriologic examination of involved lymph nodes, the tuberculin reaction and the presence or absence of frank tuberculosis in patients dying of Hodgkin's disease, all must be taken into consideration. The results of tuberculin reactions in one series of cases is to be reported.² Cultural and animal experiments on the same series will be reported subsequently. The present paper is concerned only with the co-existence of tuberculous lesions and the various forms of malignant lymphoma, including Hodgkin's disease.

Sternberg¹ found that 8 of his 13 autopsied cases of Hodgkin's disease had also tuberculous lesions, and he regarded Hodgkin's disease as a peculiar form of tuberculosis characterized by the formation of a unique type of granulation tissue. Longcope,³ however, found no tuberculosis in his 4 autopsied cases, and concluded from this and other considerations that one could not assume that tuberculosis is the cause of Hodgkin's disease. He believed that when tuberculosis occurred in combination with Hodgkin's disease it should be regarded as a secondary infection and of no etiologic importance whatever.

Weber⁴ acknowledged the frequent association of the two diseases and felt that they were probably more frequently combined in childhood than in adult life, but he, again, regarded the tubercle bacillus as a secondary invader which found in the granulomatous tissue of Hodgkin's disease an unusually favorable soil for active growth.

Yamasaki,⁶ who found tuberculosis in 4 of his 6 cases, regarded the tubercle bacillus as a secondary invader, as did Weber.

Lubarsch⁵ admitted that the association of the two diseases was too frequent to be accidental, but he was never able to recover tubercle bacilli from his cases. He pointed out, however, that they might be recovered on animal inoculation even though active tuberculosis could not be demonstrated at autopsy. In this he is supported by Pizzini,⁷ who frequently produced tuberculosis in guinea pigs inoculated with bronchial lymph nodes from patients dying without any evidence of active tuberculosis.

Lichtenstein⁸ found active tuberculosis in 7 of his 18 autopsied cases and healed tuberculosis in 3 more. He appears to be the first author to sharply distinguish between healed and active tuberculosis—a point of no small importance as will be seen later. Lichtenstein reviews the literature most thoroughly, and he concludes from his own studies that the frequency of the association of the two diseases, the intermingling of the lesions microscopically and the production in guinea pigs of tuberculosis when injected with apparently pure Hodgkin's disease nodes justify the opinion that this disease is due to tuberculosis.

Brandt⁹ found tuberculosis in 5 of his 14 cases, but he did not ascribe etiologic importance to the bacilli.

Finally, Twort,¹⁰ after a careful consideration of 61 cases, came to the conclusion that "the etiology of lymphogranuloma still remains obscure to us." He could "demonstrate consistently no specific animal or vegetable parasite in the diseased tissues either by direct microscopic examination, cultivation or animal injection." He found, "contrary to what is usually taught," only rare association with tuberculosis—in fact, in only 3 of his 27 autopsied cases did he find evidence of this condition.

One can, therefore, find in the literature opinions that support almost any point of view and the situation is not made more clear by the statement by Lemon,¹¹ that, on the basis of Roentgen ray examination, in only 8 of his 191 cases was there evidence of tuberculosis.

In view of the conflicting evidence in the literature, it seemed wise to review the material from our own clinics and to compare, furthermore, the incidence of tuberculosis in Hodgkin's disease with that in other types of malignant lymphoma—lymphocytoma, lymphosarcoma, lymphatic leukemia—and in other types of fatal disease, including myelogenous leukemia.

For this purpose all the autopsied cases of malignant lymphoma and myelogenous leukemia at the Boston City Hospital, the Peter Bent Brigham Hospital and the Children's Hospital were studied (151 cases). We are greatly indebted to Dr. S. Burt Wolbach for his kindness in placing his material at our disposal. Only those cases in which complete autopsy was performed were included. In addition, the same data were obtained on 212 unselected cases of cancer of the same age distribution, 50 cases of pernicious anemia and 400 "general autopsy" cases distributed over the same period of years.

The results are tabulated on page 697. The diagnosis of Hodgkin's disease was made according to the usually accepted standards as originally laid down by Dorothy Reed and by Sternberg. The cases were rather evenly distributed throughout the decades of life. It will be noted that 1 case had both lymphatic leukemia and widespread Hodgkin's disease. This case has previously been reported.¹² One case of lymphocytoma also had Hodgkin's disease. These figures, which are not shown in the table for simplicity's sake, do not alter the fact that no active tuberculosis was found in any case of malignant lymphoma with or without lymphatic leukemia except Hodgkin's disease. (Tables 1 and 2.)

From the literature already alluded to above, we find that tuberculosis was found in 30 of the 78 autopsied cases of Hodgkin's disease. The available data do not justify the subdivision of these cases into active and healed tuberculosis, but we can say that 38.5 per cent of the published cases showed some form of the disease. This corresponds very closely indeed with our own figures of 33.3 per cent in 30 cases of Hodgkin's disease.

TABLE 1.—COMBINED REPORTS FROM AUTOPSIES AT THE BOSTON CITY HOSPITAL, THE PETER BENT BRIGHAM HOSPITAL AND THE CHILDREN'S HOSPITAL.

Disease.	Number.	Absent.	Present.	Active.	Healed.	Per cent total tuberculosis.
<i>Total Tuberculosis.</i>						
General	400	323	77	44	33	19.3
Cancer	212	181	31	12	19	14.6
Hodgkin's	30	20	10	6	4	33.3
Lymphosarcoma	13	9	4	0	4	30.8
Lymphatic leukemia . .	30	27	3	0	3	10.0
Lymphocytoma	5	4	1	0	1	20.0
Reticulum-cell sarcoma	14	11	3	0	3	21.4
Myelogenous leukemia	50	40	10	5	5	20.0
Myeloma	6	5	1	0	1	16.6
Pernicious anemia . .	50	42	8	0	8	16.0
<i>Active Tuberculosis.</i>						
General	400	44	..	11.0
Cancer	212	12	..	5.7
Hodgkin's	30	6	..	20.0
Lymphosarcoma	13	0	..	0.0
Lymphatic leukemia . .	30	0	..	0.0
Lymphocytoma	5	0	..	0.0
Reticulum-cell sarcoma	14	0	..	0.0
Myelogenous leukemia	50	5	..	10.0
Myeloma	6	0	..	0.0
Pernicious anemia . .	50	0	..	0.0
<i>Healed Tuberculosis.</i>						
General	400	33	8.3
Cancer	212	19	9.0
Hodgkin's	30	4	13.3
Lymphosarcoma	13	4	30.8
Lymphatic leukemia . .	30	3	10.0
Lymphocytoma	5	1	20.0
Reticulum-cell sarcoma	14	3	21.4
Myelogenous leukemia	50	5	10.0
Myeloma	6	1	16.6
Pernicious anemia . .	50	8	16.0

TABLE 2.—DISTRIBUTION IN ORGANS OF LESIONS OF ACTIVE TUBERCULOSIS AND HODGKIN'S DISEASE.

Autopsy No.	Tuberculosis alone.	Hodgkin's disease alone.	Hodgkin's disease and tuberculosis.
A 23-54	Lung, spleen, adrenal, intestine, brain	Liver	Lymph nodes.
A 28-319	Lung, pancreas, intestine, marrow	0	Spleen, liver, lymph nodes.
A 28-148	Lung	Stomach	0
U 28-18	Intestine	Liver, spleen, marrow, lymph nodes	Lung.
A 28-246	Lung, spleen, adrenal, intestine	Liver	Lymph nodes.
A 30-253	Intestine	Liver, adrenal, lymph nodes, marrow	Spleen.

Carlson and Bell¹⁵ published an analysis of tuberculosis in cancer, heart disease and general autopsies. Our figures agree closely with theirs. In general autopsies we found 19.3 per cent total tuberculosis as against their 17.3 per cent, and in cancer we found healed tuberculosis in 9 per cent of the cases against their finding of 8.6 per cent. These statistical similarities are brought out to indicate that the accuracy with which tuberculosis was diagnosed postmortem in our series approximates that of another large clinic.

From the data obtained in our own series it would appear:

1. That the percentage of total tuberculosis, both healed and active, is significantly greater in Hodgkin's disease (33.3) than in other types of lymphoma (5.3) or in cancer (14.6) or general autopsies (19.3).

2. That the percentage of active tuberculosis in Hodgkin's disease (20) is very markedly greater than in the other types of lymphoma (0) or in pernicious anemia (0), cancer (5.7) or general autopsies (11).

3. That the percentage of healed tuberculosis does not materially differ in the various types of lymphoma.

4. That while cases of myelogenous leukemia have an approximately normal percentage of active tuberculosis, we found no case of pure lymphoma associated with active tuberculosis. In previous studies this fact has not been emphasized, if, indeed, it has been noted at all. It would appear to be just as significant as the association of tuberculosis with Hodgkin's granuloma.

We have found, therefore, an incidence of active tuberculosis in Hodgkin's disease far in excess of that in either the general autopsies or in other types of malignant lymphoma. It is generally acknowledged that the pathologic picture of Hodgkin's disease is distinct. If it be assumed that the tubercle bacillus is of etiological importance in Hodgkin's disease, one of two postulates must be made. Either the tubercle bacillus is not of the usual pathogenicity or the host differs in some way so that the conventional tubercle bacillus produces a fatal granuloma rather than the usual tuberculous process. If the former be the case we are faced with the very unusual fact that a large number of these Hodgkin's disease cases are invaded by both types of tubercle bacilli. If the latter assumption be made we must explain why the host reacts in two different ways to the same organism at the same time. It would seem to us that the frequent association of the two diseases indicates merely that the one predisposes to the other or that the same constitutional type is subject to both.

The explanation of the extremely low incidence of active tuberculosis in other forms of malignant lymphoma is difficult. It may possibly lie in the presence throughout the body of very large numbers of lymphocytes—well-known antagonists of the tubercle bacilli.

Conclusions. Hodgkin's disease has a much greater incidence of associated tuberculosis than is found in general autopsies, pernicious anemia or cancer.

In our experience malignant lymphoma of other types (not Hodgkin's disease) is never associated with *active* tuberculosis. This latter point has hitherto not been emphasized.

REFERENCES.

1. Sternberg, C.: Ueber eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des lymphatischen Apparates, *Ztschr. f. Heilk.*, 1898, **19**, 21.
2. In press.
3. Longcope, W. T.: On the Pathology of Hodgkin's Disease with a Report of a Series of Cases, *Bull. Ayer Clin. Lab. Penn. Hosp.*, 1903-1904, **1**, 4.
4. Weber, F. P.: Acute Cases of Hodgkin's Disease (Lymphadenoma) and the Diagnosis of the Disease from Syphilis, Tuberculosis and Atypical Leukemia, *St. Barth. Hosp. Rep.*, 1908, **43**, 81.
5. Lubarsch, O.: Ueber Lymphogranulomatose, *Berl. klin. Wchnschr.*, 1918, **55**, 708.
6. Yamasaki, M.: Zur Kenntnis der Hodgkinschen Krankheit und ihres Ueberganges in Sarkom, *Ztschr. f. Heilk.*, 1905, **25**, 269.
7. Pizzini, D. L.: Tuberkelbacillen in den Lymphdrüsen Nichttuberkulöser, *Ztschr. f. klin. Med.*, 1892, **21**, 329.
8. Lichtenstein, A.: Untersuchungen über die Aetiologie der Lymphogranulomatosis (Sternberg), *Frankfurt. Ztschr. f. Path.*, 1921, **24** (Ergnznghft.), 529.
9. Brandt, M.: Beitrag zur pathologischen Anatomie der Lymphogranulomatose, *Virchow's Arch. f. path. Anat.*, 1929, **272**, 400.
10. Twort, C. C.: Aetiology of Lymphadenoma; Summary of 6 years Researches, *J. Path. and Bact.*, 1930, **33**, 539.
11. Lemon, W. S.: Tuberculosis as an Etiologic Factor in Hodgkin's Disease. A Historical Review, *Am. J. Med. Sci.*, 1924, **127**, 178.
12. MacMahon, H. E., and Parker, F., Jr.: Case of Lymphoblastoma, Hodgkin's Disease and Tuberculosis, *Am. J. Path.*, 1930, **6**, 367.
13. Carlson, H. A., and Bell, E. T.: Statistical Study of Occurrence of Cancer and Tuberculosis in 11,195 Postmortem Examinations, *J. Cancer Res.*, 1929, **13**, 126.

A VALUABLE SIGN IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE ABDOMINAL MALARIA.

By K. P. A. TAYLOR, M.D., F.A.C.S.

HAVANA, CUBA.

DURING 5 years' hospital surgical practice in the Caribbean littoral (Colombia, Panama and Guatemala), the writer has kept records of all cases of malaria or suspected malaria in which vomiting or other acute abdominal symptoms were prominent. A tropical surgeon had early admonished that confusion and error marked the efforts of surgeons from temperate zones to differentiate acute abdominal catastrophes demanding surgical intervention from the more violent abdominal manifestations of tropical malaria.

In examining the records, it is enlightening to find that they total only 25 cases, compiled in regions where the malaria morbidity is

enormous (the community thick-film positive index being not infrequently as high as 35 per cent) and the malaria death rate probably as high as that in any part of the world. Of these cases, 16 yielded positive smears for malaria parasites in the peripheral blood, 6 had negative smears but have been classified as cases of malaria because of response to quinin and other indications to be discussed, and 3 were diagnosed as malaria on admission but proved to be acute surgical cases. In addition to these 3, of 16 patients with positive smears, 1 had an acute surgical lesion (spontaneous rupture of the spleen). It is evident, therefore, that the problem of differential diagnosis between abdominal malaria and the surgical conditions does not present itself with great frequency in these malaria-infested regions.

Presence of Occult Blood in Vomitus and Absence of Involuntary Rigidity Characteristic of Abdominal Malaria. Two clinical signs of great significance characterize the cases of abdominal malaria under discussion. These are the presence of macroscopic or occult blood in the gastric contents or vomitus during acute paroxysms of the disease, and absence of the "*sine qua non*" of peritoneal inflammation—involuntary abdominal rigidity. Of the 21 cases of malaria, all but 3 (85 per cent) showed blood in the gastric secretion. Of the 3 cases without this sign, 2 had been under quinin therapy for several days before the gastric examination was made, and the third, although vomiting had occurred for 8 days, had no other abdominal signs and probably did not have an abdominal form of malaria. In none of the cases was there actual involuntary muscular rigidity of the abdomen. The importance of these diagnostic signs (particularly the finding of occult blood) has not previously been emphasized. James,¹ Deaderick and Thompson,² Byam and Archibald,³ Manson-Bahr⁴ and Masters⁵ have reported the finding of blood in the gastric contents or stools of malarial sufferers. These writers, however, ascribe this sign as a characteristic of the algid type of malaria, rather than of the abdominal variety. James describes the finding of "small hemorrhages into the tissues of the mucosa and villi" and "patches of necrosed epithelium." Businco⁶ attributed the gastralgia and bloody vomitus observed in some cases of chronic malaria to erosion of gastric mucosa, while Castellani and Chalmers⁷ note the similarity of these symptoms to those of carcinoma.

Absence of Rigidity in Abdominal Malaria. The writer has never observed true abdominal rigidity in uncomplicated cases of the type under discussion. In this assertion he is not supported by some observers. Demjanow⁸ in reporting upon 7 cases of "malarial appendicitis" found rigidity in all. None of these cases, however, were operated upon, so that confirmation of the diagnosis is lacking. In 2 of the patients who died of malaria, postmortem microscopic examination of the appendices revealed thrombi of malarial pigment, enlargement of the lymphatic structures and infiltration of the sub-

mucosa and mucosa. Obviously, pathologic changes of this nature predispose the appendix to gangrene or pyogenic infection. Under such circumstances, one should not hesitate to operate if pain and rigidity are persistent, the leukocyte count is considerably increased, or nonfilamented neutrophils make their appearance in the peripheral blood in significant numbers. DePenning⁹ reports 2 cases of supposed malarial appendicitis with slight rigidity, unoperated. Castellani and Chalmers (*loco citato*) have also observed rigidity in malarial appendicitis.

It is significant that these claims for rigidity in abdominal malaria are all based upon cases of appendiceal involvement. Preëxisting or impending bacterial invasion of the appendix cannot be excluded in such reports.

Sporulation of malaria parasites in other abdominal viscera, notably in the liver, pancreas and spleen, is not definitely on record as a cause of rigidity. Cignozzi¹⁰ states that the liver and gall bladder are almost constantly attacked by malaria. Acute gastrointestinal manifestations of this disease are discussed by Biddan,¹¹ Martini,¹² Uduondo with Sanguinetti,¹³ and Jahavery.¹⁴ None of these investigators report the finding of abdominal rigidity, even in cases of malarial appendicitis. The presence of blood in the stools is frequently noted. There are no references, however, to the test for occult blood in vomitus or material obtained for gastric analysis. Uduondo attests the finding of necrosis of lymph follicles and Peyer's patches at autopsy. According to this writer, the response to test meal in malaria is characterized by hypochlorhydria, bile and mucus. Examinations for occult blood were not performed. (An interesting parallel is seen in Businco's description of the typical radiographic stigmata of chronic malaria—atonic gastrectasis, ptosis of the pylorus and hypomotility.)

Rieux¹⁵ lists the following conditions as most liable to be confused with abdominal forms of malaria: appendicitis, biliary infections, urinary sepsis and complications of dysentery and typhoid fever. He calls attention to the value of the therapeutic test with quinin, and states that there are no "quinin resistant" parasites. It is well recognized, however, that overwhelming malarial infections respond indifferently to quinin.

Abdominal Forms of Malaria With Occult Blood in the Vomitus. The following cases are characteristic in history, symptomatology, physical findings and examination of gastric secretion.

Case Reports. CASE 3.—Native male, aged 34 years, had fever, vomiting and pain in his spleen for 2 days. He was slightly jaundiced. Examination of his abdomen was negative except for moderate splenic enlargement. The admission temperature was 101° F. Blood count disclosed erythrocytes 2,410,000, hemoglobin 40 per cent, leukocytes 8100. The vomitus was bile-stained and yielded a positive test for occult blood. Examination for malaria parasites revealed estivo-autumnal crescents.

TABLE I.—ANALYSIS OF CASES REQUIRING DIFFERENTIAL DIAGNOSIS BETWEEN ABDOMINAL MALARIA AND ACUTE SURGICAL LESIONS.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary diagnosis.	Course.	Gastric contents.	Revised diagnosis.
1	Native, aged 19	Fever, vomiting, abd. pain	7 days	Generalized abd. tenderness	E. A. rings	Malaria	Recovered	Occult blood xx Epith. cells xx Leukocytes x R. B. C. x Bile xx	E. A. malaria.
2	Native, aged 31	Chills and fever, abd. pain, vomiting	4 months	Enlarged liver and spleen	E. A. rings	Malaria	Recovered	Occult blood xx R. B. C. x Bile x	E. A. malaria.
3	Native, aged 34	Fever, vomiting, pain in spleen	2 days	Anemia; jaundice; enlarged spleen	E. A. crescents	Malaria	Intramuscular quinine; relapse 6th day; transfusion; recovery.	Occult blood x Bile x	E. A. malaria.
4	Native, aged 17	Fever, vomiting, abd. pain	2 weeks	Enlarged spleen	E. A. rings	Malaria	Recovered	Occult blood x Mucus x	E. A. malaria.
5	Negro, aged 22	Fever, abd. pain, vomiting, constipation	3 days	Incarcerated inguinal hernia	E. A. rings	Strangulated hernia; peritonitis	Recovered	Occult blood xxx Bile x	E. A. malaria.
6	Native, aged 50	Fever, vomiting	3 days	Enlarged spleen	Tertian rings	Malaria	Recovered	Occult blood x Epith. cells xxx Leukocytes xx R. B. C. x Bile x	Tertian malaria.
7	Native, aged 34	Fever, vomiting, abd. pain	4 days	Tenderness upper abd., prostration, cyanosis	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes xx Mucus xxx Bile x	E. A. malaria.
8	Native, aged 21	Headache, vomiting, fever	5 days	Medical shock; abd. tenderness	E. A. rings and crescents	Malaria	Recovered	Occult blood x Mucus x Leukocytes x	E. A. malaria.
9	Native, aged 15	Fever, cough, abd. pain	2 days	Coryza	E. A. rings	Malaria	Recovered	Occult blood xx Leukocytes x Mucus xx	E. A. malaria.
10	Native, aged 38	Fever, vomiting	5 days	Prostration	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes x Mucus x Bile x	E. A. malaria.
11	Native, aged 28	Fever, headache, vomiting	3 days	Abd. tenderness; collapse	E. A. rings	Malaria	Recovered	Occult blood x Leukocytes x Mucus x Bile x	E. A. malaria.
12	Native, aged 31	Fever, vomiting, abd. pain	5 days	Palpable spleen	E. A. rings	Malaria	Recovered	Occult blood xxx Leukocytes x Mucus x Bile x	E. A. malaria.

TABLE 2.—CLINICAL MALARIA WITH NEGATIVE BLOOD SMEAR.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary Diagnosis.	Course.	Gastric contents.	Revised diagnosis.
13	Native, aged 18	Fever, epigastric pain, vomiting	6 days	Epigastric tenderness	Negative	Malaria	Recovered	Occult blood xxx Leukocytes xx Epith. cells xx Bile xxx	Malaria.
14	Native, aged 29	Fever, chills, vomiting	8 days	Enlarged spleen; anemia	Negative	Malaria	Transfusion; recovered	Occult blood x Bile x	Malaria.
15	Native	Fever, abd. pain, vomiting	3 days	Abd. tenderness and distention; jaundice; prostration	Negative	Malaria or yellow fever	Death 2d day. Aut.: toxic hepatitis, enlarged spleen, neg. smears from liver and spleen	Occult blood x	Malaria.
16	Italian, aged 41	Fever, chills, pain in back and loins	1 month	Negative	Negative	Malaria	Hemoglobinuria on 3rd day; recovered	Occult blood x	Blackwater fever.
17	Native, aged 29	Chills, fever, vomiting	1 day	Negative	Negative	Malaria	Recovered	Occult blood x	Malaria.
18	Native, aged 18	Fever, abd. pain, vomiting	6 days	Abd. tenderness; enlarged spleen; prostration	Negative	Malaria	Algid type; T. 95.6°; constant vomiting 12 hours; active stimulation; recovery	Occult blood xxx Leukocytes x Mucus x	Malaria.
19	Negro, aged 24	Fever, chills, vomiting, abd. pain	MALARIA WITHOUT 5 days	NEGATIVE	OCCULT BLOOD E. A. rings	Malaria	Recovered	Negative	E. A. malaria.
20	Native, aged 33	Fever, abd. pain, vomiting	4 weeks	Enlarged spleen; anemia	Negative	Malaria	Recovered	Negative; had taken quinin for 6 days	Malaria.
21	White, aged 28	Fever, abd. pain, vomiting	8 days	Negative	E. A. rings and crescents	Malaria	Recovered	Negative	E. A. malaria.

TABLE 3.—SURGICAL CASES.

Case.	Status.	Symptoms.	Duration.	Physical signs.	Malaria smear.	Preliminary diagnosis.	Course.	Gastric contents.	Revised diagnosis.
22	Negro, aged 55	Vomiting, abd. pain	3 days	Abd. distention and tenderness	Negative	Malaria	Diag.: acute intes. obstruction; operation; car. of pylorus with obstruction and metastasis. Died	Occult blood xx	Carcinoma of pylorus.
23	Native, aged 19	Fever, vomiting	3 days	Abd. distention and tenderness; compound fracture of tibia, not grossly infected	Negative	Malaria	Fever; vomiting; ascariasis until death on 2d day. Aut.: anemia, dil. of left auricle, splenic hypertrophy; 22 live ascariasis; no intes. obstruction	Occult blood xxx Epith. cells x Bile xx	Ascariasis; septicemia.
24	Native, aged 19	Vomiting, pain in spleen, weakness	4 hours	Abd. distention, dullness in flanks; tenderness in spleen; intra-abd. hemorrhage	E. A. rings	Malaria	Splenectomy for rupture; auto-transfusion; death from shock and hemorrhage	Negative	Spont. rupt. of spleen; E. A. malaria.
25	Native, aged 25	Abd. pain, vomiting	3 days	Abd. distention, rigidity and mass	Negative	Malaria	Treated for malaria for 3 days; repeated purging. Aut.: perforation of 2 typhoid ulcers; general peritonitis	Negative	General peritonitis; perforation of typhoid ulcers.

The patient was given 4 intramuscular injections of quinin dihydrochlorid of 1 gm. each at 6-hour intervals. Thereafter, 1 gm. was administered by mouth at similar intervals. On the fifth hospital day the patient's temperature became normal, and the dosage of quinin was reduced to 1 gm. 3 times daily. Six days later, while 3 gm. of quinin sulphate was still being taken daily by mouth, the patient again became feverish and irrational. Vomiting recurred, with the vomitus still showing occult blood. The urine now contained 0.5 per cent albumin but no hemoglobin. No malaria parasites were found in the circulating blood. Because of the persistent occult blood reaction, intramuscular injections of quinin were resumed, and the temperature became normal on the third day. The blood count now disclosed erythrocytes of only 2,100,000 and hemoglobin of 15 per cent. Transfusion of 200 cc. of citrated blood was performed and recovery ensued without further complications.

This case presents three illustrative features: (1) enormous resistance of a malarial infection to quinin therapy; (2) the misleading finding of only a few estivo-autumnal crescents in the thick film; (3) recurrence of a severe malarial infection, with massive blood destruction, while quinin treatment was being practised. This was corroborated by the finding of occult blood in the vomitus while the blood smear remained negative.

CASE 5.—Negro male, aged 22 years, was admitted with a history of fever and chills for 3 days, accompanied by generalized abdominal pain, most severe in the upper quadrants, vomiting, constipation and headache. The temperature was 104° F, and slight delirium was evident. The admitting physician had made the diagnosis of strangulated inguinal hernia, with peritonitis. Abdominal examination was negative, except for the presence of a slightly enlarged and tender spleen. The hernia was incarcerated (probably as a result of constant vomiting), but was reduced without difficulty. Estivo-autumnal rings were found in the thick film. The vomitus was bile-stained and contained macroscopic blood. Two days later, after quinin treatment, a test meal yielded bile, no occult blood, and occasional leukocytes and epithelial cells. The temperature was normal and vomiting had stopped on the second day.

Inferential Diagnosis of Malaria by Presence of Occult Blood. The clinical existence of acute forms of tropical malaria with one or more negative blood smears is not uncommon. Elucidation of the reasons for the occurrence of this paradox does not lie within the scope of the present paper. Intermittent or irregular self-treatment with quinin is probably the commonest cause of failure to find parasites in the peripheral blood. A certain percentage of such cases, in which acute manifestations of sporulation in the abdominal viscera make their appearance, may be diagnosed tentatively as malaria by the finding of occult blood in the vomitus. The correctness of this interpretation is signified by the course of events in the following case records:

CASE 14.—Native male, aged 28 years, was reputed to have had fever, chills and vomiting for 8 days. His condition appeared very unfavorable. He was vomiting constantly. The erythrocyte count numbered only 1,800,000, with hemoglobin 20 per cent. Urine examination was negative, as were both thick and thin blood films. The spleen was considerably

enlarged, but other abdominal signs were absent. Fever of 103° F. was experienced.

Analysis of the vomitus revealed occult blood and bile. The patient was given 0.5 gm. doses of quinin dihydrochlorid with adrenalin 0.7 cc. Slight improvement was noted the next day, but blood was still present in the vomitus. Horse serum failed to check this diapedesis. Transfusion of 400 cc. of citrated blood had the desired effect, however. On the sixth day the temperature became normal.

CASE 15.—Native male, aged 19 years, had fever, pain in the abdomen and vomiting for 3 days before admission. This was a recurrence of similar symptoms which had existed intermittently for a number of weeks, and had been treated with small doses of quinin.

The patient was extremely prostrated and jaundiced. His abdomen was universally tender and slightly distended. Blood examination for malaria parasites was negative. The vomitus contained occult blood, but was not of the character observed in yellow fever. Urine examination was negative save for the presence of bile pigments. The temperature rose to 104.2° F.

Active stimulation and quinin injections were utilized. The patient vomited copiously before dying on the second hospital day. Postmortem examination was entirely negative save for the manifestations of jaundice, toxic hepatitis, and the presence of splenic enlargement grade two. Smears from the liver and spleen failed to reveal malarial parasites. Smears from bone marrow were not made. Weil's disease, yellow fever and septicemia suggest themselves as alternative diagnosis. The history of this patient before coming to the hospital was that of malaria. On two previous admissions within a year he had positive blood smears.

Abdominal Malaria Without Occult Blood. Three cases of malaria with acute abdominal symptoms were observed to have the gastric secretion free of occult blood. In 2 of these, the analysis was made after several days of quinin treatment.

Nonmalarial Surgical Cases With and Without Occult Blood. Four additional cases are recorded which illustrate the fallibility and also the usefulness of the occult blood test in distinguishing surgical from malarial abdominal cases. In all of these, the preliminary diagnosis upon admission was malaria.

Spontaneous Rupture of the Spleen. CASE 24.—Native male, aged 19 years, was seen in consultation 18 hours after admission in the hospital. Because of his collapsed condition no direct history was obtainable. He had been picked up in an apparently fainting condition in the shop where he was at work. He was not seen to have been struck or injured, and had appeared to be in ordinary health.

On entering the hospital, it was noted that the patient's spleen extended below the anterior superior iliac spine. The patient complained of pain in the splenic area, nausea and weakness. The temperature was 98.1° F.; pulse, 94; respiration, 24. Blood examination revealed estivo-autumnal rings. Routine treatment for malaria was instituted. Shortly after admission the patient vomited bile-stained fluid. This was negative for occult blood.

When seen by me, the patient was restless; the pulse, 130; temperature, 97.4° F.; respiration, 30. The extremities were cold. There was considerable abdominal distention, and dullness could be percussed in both flanks. Pain in the spleen was constant and severe. Vomiting had occurred on two succeeding occasions, the vomitus in each case being free of occult blood. A needle was inserted into the abdominal cavity in the left iliac region, and 20 cc. of dark blood were aspirated. The diagnosis of splenic rupture was made. On the operating table, intravenous infusion was started before the abdomen was opened. A large stellate rent was disclosed

on the diaphragmatic surface of the spleen. While large quantities of blood were retrieved from the abdomen, citrated and infused, the spleen was freed with difficulty from numerous adhesions, and removed. The patient succumbed to shock and hemorrhage. Delay in operating probably caused this fatality.

Conclusions. 1. The great majority of sufferers from tropical malaria with acute abdominal symptoms in this study were infected with estivo-autumnal parasites (93 per cent).

2. Of this number, a high percentage (85 per cent) revealed positive tests for occult blood in the vomitus or gastric contents. The finding of occult blood was of considerable value in establishing the diagnosis of abdominal malaria.

3. The distinction of acute abdominal malaria from acute surgical lesions of the abdomen rests principally upon physical signs, of which the most important is absence of rigidity in malaria.

REFERENCES.

1. James, S. P.: *Malaria at Home and Abroad*, John Bale Sons, London, 1920, p. 140.
2. Deaderick, W. H., and Thompson, L.: *Endemic Diseases of the Southern States*, Philadelphia, W. B. Saunders Company, 1916, p. 116.
3. Byam, W., and Archibald, R. J.: *The Practice of Medicine in the Tropics*, Henry Froude, Hodder & Stoughton, London, 1922.
4. Manson-Bahr, P. H.: *Tropical Diseases*, Cassell & Co., London, 1921, p. 45.
5. Masters, W. E.: *Essentials of Tropical Medicine*, John Bale Sons, London, 1920, p. 99.
6. Businco, O.: *Le Gastro-enteropatie dei Malarici Chronici*, *Riforma med.*, 1929, 45, 1142.
7. Castellani, A., and Chalmers, A. J.: *A Manual of Tropical Medicine*, London, 1919, p. 1177.
8. Demjanow, G. S.: *Ueber die Appendicitis malarica*, *Centralbl. f. Bakt.*, 1926, 100, 348.
9. De Penning, H.: *Malaria and Appendicitis*, *Brit. Med. J.*, 1928, 1, 53.
10. Cignozzi, O.: *Malaria and Gallstones*, *Abs., J. Am. Med. Assn.*, 1919, 85, 934.
11. Biddan, I.: *Perniciosa malarica che simula una peritonitis acuta*, *Gazz. de Osp.*, 1929, 50, 1326.
12. Martini, V.: *Colica appendicolare de origine malarica*, *Cultura Med. Mod.*, 1930, 9, 101.
13. Uduando, C., and Sanguinetti, L.: *Gastroenteropatii Paludicas*, *Los progresos de la Clínica*, 1926, 23, 623.
14. Jhaveri, M.: *The Gastro-intestinal Type of Malaria*, *Indian Med. Gaz.*, 1926, 61, 26.
15. Rieuz, J.: *Le Pseudo Paludisme*, *J. rev. gén. de chir. et de thérap.*, 1928, 42, 369.

A STUDY OF THE PATHOGENESIS OF MYOCARDIAL FIBROSIS ("CHRONIC FIBROUS MYOCARDITIS").

BY MADELAINE R. BROWN, M.D.,

OUT-PATIENT PHYSICIAN, DEPARTMENT OF NEUROLOGY, BOSTON CITY HOSPITAL.

(From the Department of Pathology, Johns Hopkins University, Baltimore, Md.)

It has long been known that in many severe infectious diseases such as typhoid fever, diphtheria and scarlatina, acute focal myocarditis may be present; but it seems important to determine

whether these acute infections play any rôle in the production of the myocardial scars seen frequently at autopsy. O'Hare¹ states that Assman and other German writers, Osler and most authors of current textbooks on the subject believe that acute infections, especially diphtheria and rheumatic fever, are common causes of chronic myocarditis, and Fahr² finds that the general practitioner believes that foci of infection are largely responsible for chronic muscular incompetency of the heart in which there is no other obvious cause. Brooks,³ from the analysis of a large number of autopsies, ascribes the scarring of the muscle to a great variety of causes.

There has been much misunderstanding of the term "chronic myocarditis." For the clinician it means myocardial insufficiency, as evidenced by the poor quality of the heart sounds and decompensation; while the pathologist uses it to describe areas of fibrous tissue in the myocardium. A more accurate term would be "scarring of the myocardium" or "myocardial fibrosis."

Material. The material for this study consisted of 1000 consecutive autopsies (7000 to 7999) from this department, of which 110 described areas of scar tissue in the myocardium. Various changes were found in the myocardium in 81 other cases but there was no evidence available to show that these might ultimately be related to myocardial scarring. The only useful material for analysis was that in which actual scarring was found and the following is an attempt to recognize the course of events in those 110 cases.

This group, in which the scarring varied in extent from fibrous areas seen only under the microscope to great scars involving a large part of the left ventricle, included especially arteriosclerotic and syphilitic cases. A tabulation shows the following:

TABLE 1.—ANALYSIS OF 110 CASES OF MYOCARDIAL SCARRING.

59	Generalized arteriosclerosis: 6 with syphilis not involving heart or aorta, 52 showing advanced coronary sclerosis, 3 with normal coronaries and 4 with no report.
24	Syphilitic aortitis: 15 of these showed coronary sclerosis, 7 had normal coronaries and 2 with no report, 2 also with arteriosclerosis and hypertension.
15	Rheumatism: of these 2 had coronary sclerosis, 12 normal coronaries and 1 with no report.
12	Miscellaneous: 3 had a <i>Streptococcus viridans</i> endocarditis, of which 2 were on a basis of old rheumatism but with normal coronaries, 1 had chronic aortic endocarditis, probably rheumatic, 4 had generalized tuberculosis, 1 chronic nephritis and there were 3 others in which the coronaries seemed unchanged or attracted no notice.

Thus, in 110 cases, 98 were plainly associated with arteriosclerosis, syphilitic aortitis or rheumatism, while of the 12 others, 3 at least gave evidence of old healed rheumatism, 4 were cases of tuberculosis, 1 chronic nephritis, while 3 were children in whom the process was probably quite different.

It seems that the possible causes of scarring in the myocardium may be classified as follows:

1. Focal infectious myocarditis. (a) acute; (b) chronic.
2. Toxic myocarditis.
3. Interference with the blood supply. (a) Thrombosis or embolism; (b) ischemic necrosis from slow reduction of blood supply.

Focal Infectious Myocarditis. In the present series of 1000 cases the clinical histories of those with and without chronic fibrous myocarditis gave, of course, frequent evidence of such infectious diseases as pneumonia, typhoid fever, diphtheria, scarlatina and malaria. Since these were quite as common in the 890 cases in which there was no scarring, it seems impossible to ascribe the scarring to them in the present series.

In the group recognized as syphilis and rheumatism the question arises as to whether the sclerosis followed a previous focal myocarditis. Warthin,⁴ in a series of 41 cases of syphilis, found 36 active lesions in the heart and 32 in the aorta. He defines active lesions as those in which spirochetes or characteristic tissue lesions are present. Brooks,⁵ in a series of 50 autopsies on luetic hearts, found changes in 44. Fibroid changes were present in 14, gummata in 5, and true myocarditis with infiltration of leukocytes in 6 cases of which 5 also showed scar tissue.

Of the 24 syphilitic hearts showing myocardial fibrosis in this series, only 6 gave evidence of any infiltration of leukocytes and no spirochetes were found. In 3 cases there was perivascular infiltration and fresh scars were present. In 2, lymphocytes were found about necrotic areas. It seems probable, therefore, that local syphilitic lesions may play a part in producing myocardial scars.

The cases of rheumatic fever present a similar problem as to the pathogenesis of the scar tissue. It is our common experience (MacCallum⁶) that the remains of Aschoff bodies may be recognized for a long time, as scar-like thickenings of the adventitia and periadventitial tissue about the branches of the coronary arterioles. Occasionally, in the earlier stages, small foci of necrosis of the muscle fibers may be seen but in the end no extensive scarring appears to result and even the perivascular thickenings contract and tend to disappear. Slater⁷ quotes Aschoff as stating that he believed they cleared up. Slater himself writes that he believes all myocardial scars in rheumatic heart disease are due either to invasion of the vessel or its constriction following periarterial infiltration (Aschoff bodies) and not primarily to focal myocarditis.* In this series there were 15 rheumatic hearts with minor scarring of the myocardium.

Toxins. Fleischer and Loeb⁸ produced experimental myocarditis in 60 per cent of their rabbits with spartein sulphate, caffein and

* It should be recognized, however, that many competent pathologists regard the (perhaps extensive) myocardial scarring of rheumatic cases with normal coronaries as evidence either of a "myocarditis proliferans" or of fibrous replacement of muscle fibers degenerated by the disease process.—EDITOR'S NOTE.

adrenalin injected intravenously, but 5 months later all changes had disappeared except a few small scars. Stewart⁹ produced rather extensive scarring of the heart wall with adrenalin injections. None of the cases in the present series gave evidence of having suffered the effects of any known toxin.

Interference With the Blood Supply. Hunter¹⁰ states that arteriosclerosis of the coronary arteries must explain the whole picture of chronic fibrous myocarditis. Brooks⁵ found coronary disease in 35 of his 40 syphilitic cases with myocardial changes. He thinks the myocardial degenerations depend upon primary alterations in the coronaries which form a striking feature of the disease. Slater⁷ states that in rheumatism the healing of the arteritic and periarteritic foci can cause such sclerotic narrowing of the arterioles that ischemic necrosis may result and that all scars are due either to plugging of the vessels from thrombi or to anemic necrosis from their constriction.

As may be seen from the tabulation of the cases in this series given above, almost all the cases in which there were myocardial scars showed changes in the coronary arteries, although there were also cases of coronary disease without any myocardial scarring.

The rheumatic group shows the least coronary disease and the least myocardial scarring, although in those occasional cases in which there was marked coronary sclerosis there was also a correspondingly extensive scarring. Among the syphilitic cases in general there were some with complete occlusion of the coronary lumen, especially near or at its mouth, others with more extended sclerosis of the coronary and thrombosis. But there were 18 cases of syphilitic aortitis in which there was neither scarring of the heart nor coronary disease. The arteriosclerotic cases which form the great bulk of the whole group, 59 of the 110 cases, show every degree of distortion and narrowing of the coronary arteries, often with calcification and complete occlusion in which terminal thrombosis plays a part.

Gross¹¹ has made beautiful injections of the coronaries in normal hearts in various decades of life and finds that the older the patient, the better adapted is the heart to receive the brunt of the obliteration, even of a main coronary, not only on account of the development of abundant and free anastomoses, but also from the formation of a dense feltwork of arterial telæ adiposæ. This may perhaps affect the numerical relation of the rheumatic and syphilitic cases to the arteriosclerotic since the latter usually occur in much older people.

Conclusions. In this series of 1000 cases it is not evident that infectious diseases or toxins give rise directly to fibrosis of the myocardium, although they may be concerned in producing arteriosclerosis of the coronary arteries.

Direct invasion of the heart muscle in syphilis and rheumatism plays a minor rôle in the pathogenesis of myocardial scarring.

Disease of the coronary arteries, which was present in 70 of the 110 cases, causing either infarction or more slowly produced ischemic necrosis of the muscle fibers, is advanced as the important etiologic agent of myocardial scarring ("chronic fibrous myocarditis").

NOTE.—I am indebted to Dr. W. G. MacCallum for his assistance in examination of the material and advice in preparation of the paper.

BIBLIOGRAPHY.

1. O'Hare, J. B., Calhoun, A. W., and Altnow, H. O.: Etiology of Chronic Myocarditis, *J. Am. Med. Assn.*, 1928, **90**, 1436.
2. Fahr, G.: Etiology of the Chronic Heart Muscle Diseases of Frequent Occurrence in General Practice, *Minnesota Med.*, 1926, **9**, 5.
3. Brooks, H.: Degenerative Diseases of the Heart Muscle: Its Cause, Types and Diagnosis, *Am. Pract.*, 1913, **47**, 395.
4. Warthin, A. S.: The Persistence of Active Lesions and Spirochetes in the Tissues of Clinically Inactive or "Cured" Syphilis, *Trans. Assn. Am. Phys.*, 1914, **29**, 416.
5. Brooks, H.: A Study of the Heart in Syphilis, *Med. Rec.*, 1912, **81**, 351.
6. MacCallum, W. G.: Textbook of Pathology, 3d ed., Philadelphia, W. B. Saunders Company, 1924, p. 571.
7. Slater, S.: Involvement of the Coronary Arteries in Rheumatic Fever, *Am. J. Med. Sci.*, 1930, **179**, 22.
8. Fleischer, M. S., and Loeb, L.: Experimental Myocarditis, *Arch. Int. Med.*, 1909, **3**, 78; Further Investigations in Experimental Myocarditis, *Arch. Int. Med.*, 1910, **6**, 427.
9. Stewart, H. A.: The Mode of Action of Adrenalin in the Production of Cardiac Hypertrophy, *J. Path. and Bact.*, 1912, **17**, 64.
10. Hunter, O. B.: The Pathologic Elements Underlying Myocardial Degeneration, Cardiac Failure and Cardiac Rupture Resulting from Acute and Chronic Occlusion of the Coronary Vessels, Kober Foundation Address before the Medical Society of District of Columbia, March 27, 1926.
11. Gross, L.: The Blood Supply of the Heart, New York, P. B. Hoeber, Inc., 1921.

GALL BLADDER INFECTION AND ARTHRITIS.

BY EDWARD F. HARTUNG, M.D.,

ASSOCIATE IN MEDICINE AND CHIEF OF ARTHRITIS CLINIC,

AND

OTTO STEINBROCKER, M.D.,

INSTRUCTOR IN MEDICINE,
NEW YORK CITY.

(From the Arthritis Clinic, New York Post-Graduate Hospital and Medical School.)

THE gall bladder is frequently mentioned as a focus of infection in discussions of chronic rheumatic disease, especially in the arthritids. There is, however, a paucity of thorough, clinical studies on the subject. In order to determine the frequency and importance of gall bladder infection in chronic rheumatic disease, this study of 200 cases was undertaken.

The general principle of focal infection in its relationship to arthritis will receive no detailed attention here. It will suffice to state that we are aware of the variety of opinions on this subject.

Some workers, particularly in European centers, deny any direct relationship between focal infection and the arthritides. Others¹ feel that the widespread systemic disturbances we call rheumatic are the result of an actual bacteremia arising in a distant focus and resulting in a deposition of organisms in the affected joints, still others² that the systemic changes are the result of a general "hyper-ergic," or allergic state, the blood and joints remaining sterile. While there is a difference of opinion as to the mechanism by which a focus causes arthritis, there is in the literature an almost universal agreement on the principle of focal infection as the etiologic agent in rheumatic disease.

Poynton and Paine³ in England, Miller in Berlin, Billings in the United States, to mention a few of the workers upon whom we lean, have made extensive bacteriologic contributions to the subject of focal infection and its importance in chronic rheumatic disease. As a result of these studies, particularly in the past 10 years, the relative importance of certain foci has been emphasized. Thus Pemberton and Pierce,⁴ in one series of rheumatic cases, mention the occurrence of dental infection in 54 per cent, nose and throat and accessory sinuses in 31 per cent of the cases. Willcox⁵ found dental sepsis in 72 per cent; tonsillar in 10 per cent. Cecil and Archer⁶ found dental sepsis in 33 per cent and tonsillar in 61 per cent of their series. The incidence of gall bladder disease as a focus receives only occasional mention in a few reports. What definite part does it play, if any? Is gall bladder infection worthy of consideration as a possible etiologic agent in arthritis?

Deaver⁷ makes the statement in a passing reference, that occasionally rheumatoid arthritis may be traced directly to an infected gall bladder. Pemberton,⁸ in a study of 33 cases for gall bladder foci, after remarking on the unsatisfactory status of diagnosis of gall bladder disease along medical lines, reports the results of duodenal drainage and culture. There is no record of the number of cases of arthritis from which this series was drawn, or of the result of cholecystography.

Methods of Determining Gall Bladder Infection. In the diagnosis of gall bladder infection we have been guided by four methods of approach: (1) History, (2) Roentgen rays, (3) duodenal drainage and (4) blood chemical findings. It is not our purpose to evaluate various methods of gall bladder diagnosis. There is still contention revolving about each one of these criteria. The clinical history is considered by many to be as diagnostic as any other approach. We use this as our starting point, all patients complaining of even the mildest gall bladder symptomatology receiving further investigation.

Whether or not gall bladder disease means gall bladder infection is still in dispute. The generally accepted opinion and the bulk of evidence tends to show that the disorders are microbic in origin.

Pathologic gall bladders, therefore, as determined by Roentgen rays, are considered infected gall bladders. Cholecystography by the Graham method is now considered extremely accurate in diagnosing gall bladder disease. Thus, Graham⁹ (1926) found the method to be correct in 97.2 per cent of the cases verified at operation, Case¹⁰ (1929) claims 90 per cent accuracy, Graham¹¹ (1931) 100 per cent, Feldman¹² (1930) 94.3 per cent, Beilin and Carlson¹³ (1931) 98.3 per cent, the error in diagnosis being 1.7 per cent. Writers vary somewhat in their claims for accuracy from 78 to 100 per cent. About cases that are declared negative by cholecystography and do not come to operation we, of course, know nothing. We, ourselves, used oral administration of the dye. Intravenous administration is considered somewhat more accurate. The conclusion is that, while cholecystography does not always give evidence of stone, it is a very accurate indicator of gall bladder infection.

Duodenal drainage is of interest because of the possible bacteriologic and microscopic constituents of the bile obtained. Bacteriologically the information obtained is often questionable. In the first place the technique of sterile duodenal drainage is extremely difficult and by some is claimed to be impossible. In the second place, streptococci are often found in the normal duodenum. Third, bacteriology of the bile gives absolutely no indication of infection of the gall bladder wall. Judd, Mentzer and Parkhill,¹⁴ in 193 cases of diseased gall bladders removed at operation from which bile was aspirated, found positive cultures in only 14 per cent compared with 98 per cent of positive cultures when made from the wall of the gall bladder. Wilkie¹⁵ found the bile was sterile in the vast majority of cases of chronic cholecystitis, while Alvarez, Meyer *et al.*¹⁶ obtained positive cultures from 82 per cent of the calculous and from 57 per cent of the noncalculous gall bladder walls. The reasons for this are not quite clear, but it is suggested that the bile, especially if concentrated, is bactericidal. Certainly duodenal drainage gives no real indication of gall bladder tissue infection. Only positive findings can have a value, negative results being no index of the status of the gall bladder wall. The findings of *Bacillus coli* in the duodenum after a fast is considered indicative of infection. Microscopic findings in the bile are also in dispute. The origin of B bile has not yet been conclusively proved. Opinions run from those of Sweet¹⁷ and Halpert¹⁸ who question whether or not bile ever passes out of the gall bladder through the cystic duct, to those who claim that some gall bladder bile is obtained through the duodenal tube and that the method gives additional information, often showing trouble where gall bladders are negative to Roentgen ray. The findings considered important are cholesterol crystals, calcium and bilirubinate pigment which are indications of stone, and bile-stained pus, mucus and epithelial cells, which indicate infection. A confusing factor is that leukocytes and epithelial cells

are commonly found in the duodenum of normal patients. Emphasis is placed on whether or not these constituents are bile stained.

The blood chemistry has doubtful value. There is very little known on the relation of blood chemical findings to cholecystitis. A high cholesterol (above 200) may mean stone. The cholesterol esters usually parallel the cholesterol. Blood urea is frequently low in diseases of the bile ducts and liver.

Method. In 200 consecutive cases of chronic rheumatic disease of all types (rheumatoid arthritis, osteoarthritis, myositis and neuritis) every patient who by history and physical findings was suspected of gall bladder disease received special investigation. Of the 200 patients, 30 fell in this group. All 30 were subjected to cholecystography, using the oral administration of dye. Where any doubt arose, additional evidence was sought in duodenal drainage and blood chemistry. Dr. R. F. Carter and Dr. R. Twiss kindly coöperated with us in this phase of the work.

Findings. Twenty-five of this group of 30 patients were found to have normal gall bladder function according to cholecystography, while 5 were considered infected. Of these 25 negative cases, 13 received additional investigation by way of the duodenal tube and blood chemistry. Four of these patients, in spite of negative Roentgen-ray findings, gave positive evidence of infection by duodenal drainage. Of these 4, 3 revealed streptococci and cholesterol crystals in drainage while 1 repeatedly showed evidence of *Bacillus coli* infection. The evidence, weak as it might be in some respects, was substantiated in every case by definite clinical evidences of cholecystitis.

RHEUMATIC PATIENTS IN WHOM A DIAGNOSIS OF CHOLECYSTITIS WAS MADE.

Case No.	Cholecystography.	Duodenal, microscopic.	Drainage, bacteriologic.	Blood chemistry.	
				Urea.	Cholesterol.
73611	Pathologic	Bile pigment; calcium; cholesterol	Nonhemolytic strep.	4.7	0.217
66403	Pathologic	Bile pigment; calcium; cholesterol; bile stained w.b.c.	Staph. alb.	..	0.244
44719	Pathologic	Calcium; cholesterol	Staph. alb.	8.9	0.185
66091	Pathologic	9.7	0.191
30948	Pathologic				
48912	Negative	Calcium; bile stained w.b.c.; bile pigment	Nonhemolytic strep. Staph. alb.	7.2	0.256
81313	Negative	Cholesterol	Nonhemolytic strep.	13.1	0.175
48410	Negative	Bilirubinate pigment	Nonhemolytic strep. Staph. alb.	5.3	0.300
29281*	Negative	calcium; cholesterol	B. coli (2 drainages)	13.0	
				

* The history and physical examination in all cases supported the diagnosis of cholecystitis.

The diagnosis of the 5 found positive on cholecystography was supplemented in part by evidence from duodenal drainage. A table showing the pertinent facts in each positive case is appended. It will be seen that 9 (4.5 per cent) proved to have gall bladder disease.

Of these 9 patients, 6 had the osteoarthritic type of arthritis, whereas 3 had the type commonly considered infectious. As usual the former fell within the older age group (40 to 60 years). The average age of all 9 was 44 years. All were females. One of these 9 was subjected to cholecystectomy and was given a vaccine made from the organisms found in the duodenum. Others received repeated therapeutic drainage. In no case did these measures materially help the arthritis.

Comment. In 200 patients with chronic rheumatic disease, only 4.5 per cent gave any evidence whatever of gall bladder infection. It is of interest to compare this figure with the much higher incidence of nasal, pharyngeal and dental infection in arthritis. To compare it with the incidence of gall bladder disease in general is of even more importance. At the Mayo Clinic, in 49,659 general admissions the incidence of gall bladder disease was 5 per cent.¹⁹

The fact that all our positive cases were females is also of significance, the usual sex distribution in cholecystitis being 2 females to 1 male. Also the average age (44 years) is to be noted, and the fact that most of them have passed their menopause, since gall bladder disease ordinarily occurs in both of these groups.

Conclusion. Our study reveals that, in 200 cases of various chronic rheumatic conditions, the incidence of gall bladder infection is no higher than in any group of general hospital admissions. In no case was cholecystitis seen to be a definite factor in etiology.

BIBLIOGRAPHY.

1. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J.: Etiology of Rheumatoid Arthritis, *Am. J. Med. Sci.*, 1931, 181, 12.
2. Swift, H. F.: Rheumatic Fever, Hektoen Lecture, Billings Foundation, *J. Am. Med. Assn.*, 1929, 92, 2071.
3. Poynton, F. J., and Paine, A.: The Etiology of Rheumatic Fever, *Lancet*, 1900, 2, 861 (Fig. 5), 932 (Fig. 4).
4. Pemberton, R., and Pierce, E. G.: Clinical and Statistical Study of Chronic Arthritis Based on 1100 Cases, *Am. J. Med. Sci.*, 1927, 173, 31.
5. Willcox, Sir W.: The Diseases of the Periodontal Tissues Due to Infection in Their Relation to Toxemia: The Systemic Effects, *Brit. Dent. J.*, 1923, 44, 537.
6. Cecil, R. L., and Archer, B. H.: Classification and Treatment of Chronic Arthritis, *J. Am. Med. Assn.*, 1926, 87, 741.
7. Deaver, J. B.: Sequelæ of Biliary Tract Infection, *J. Am. Med. Assn.*, 1930, 95, 1641.
8. Pemberton, R.: Arthritis and Rheumatoid Conditions, Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.
9. Graham, E. A.: New Developments in Our Knowledge of Gall Bladder, *Am. J. Med. Sci.*, 1926, 172, 625.
10. Case, J. T.: Present Status of Roentgenologic Diagnosis of Gall Stones, *Canadian Med. Assn. J.*, 1929, 20, 380.
11. Graham, E. A.: Prevention of Carcinoma of Gall Bladder, *Am. Surg.*, 1931, 93, 317.

12. Feldman, M.: Cholecystography: Analysis of 500 Cases Observed by Means of Oral Method, *Radiology*, 1930, **15**, 675.
13. Beilin, D. S., and Carlson, G. D.: Clinical Value of Cholecystography by the Oral Method, *Radiology*, 1931, **17**, 559.
14. Judd, E. S., Mentzer, S. H., and Parkhill, E.: Bacteriologic Study of Gall Bladders Removed at Operation, *Am. J. Med. Sci.*, 1927, **173**, 16.
15. Wilkie, A. L.: Bacteriology of Cholecystitis: Clinical and Experimental Study, *Brit. J. Surg.*, 1928, **15**, 450.
16. Alvarez, W. C., and others: Gall Bladder Infections, *J. Am. Med. Assn.*, 1923, **81**, 974.
17. Sweet, J. E.: Gall Bladder: Its Past, Present and Future, *Internat. Clin.*, 1924, **1**, 187.
18. Halpert, B.: Research on Gall Bladder, *Med. Klin.*, 1924, **20**, 408.
19. Mentzer, S. H.: Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, *Surg., Gynec. and Obst.*, 1926, **42**, 782.

CARBARSONE THERAPY IN AMEBIASIS.

BY NORMAN DAVID, M.D.,

HERBERT JOHNSTONE, PH.D.,

AND

L. L. STANLEY, M.D.,

SAN FRANCISCO, CALIF.

(From the Pacific Institute of Tropical Medicine in the Hooper Foundation for Medical Research, University of California, and the San Quentin Prison, San Quentin, Calif.)

AN opportunity was afforded, by a current protozoölogic survey of new admissions to San Quentin Prison, to study the effectiveness of 4-carbaminophenyl arsonic acid (carbarsone)* in amebiasis under excellent conditions of control, in the effort to determine whether or not a previous report on the usefulness of this drug in amebiasis¹ might be confirmed. Judgment as to the effectiveness of the therapy was based on the same criteria which were generally discussed by Reed and his associates.¹

Forty-two patients have been observed, with careful and frequent stool examinations, for 3 or more months following cessation of treatment. Four other patients were paroled before such an observation period could be completed, and it was impossible to follow them satisfactorily. Two of these 4 had recurrence of stools positive for *Entamoeba histolytica* after the first course of carbarsone therapy (5 gm. in 10 days); one 6 weeks after cessation of treatment and another after 7 weeks. Both these patients had heavy infections. A second course of carbarsone therapy cleared the stools promptly, and they were negative for *Entamoeba histolytica* when the patients were paroled, both 1 month after stopping

* Supplied by Eli Lilly & Co., Indianapolis, Ind.

the second course of treatment. Another patient with a severe infection with liver involvement (No. 37, Table 1) had a recurrence of positive stools after the first course of treatment with carbarsone. This patient received another course of carbarsone, a total of 20 gm. in 7 weeks, after which his stools remained clear for 2 months and then became positive again. He had previously been treated with emetin hydrochlorid and other amebicidal agents.

TABLE 1.—RESPONSE OF PATIENTS INFECTED WITH *ENTAMEBA HISTOLYTICA* TO CARBARSONE THERAPY.*

Patient No.	Symptoms and signs.	Observation period after treatment in months.	Stools examined after treatment and found negative.	Response.
1	+	6	24	C. P.
2	—	6	23	C.
3	+	6	25	C. P.
4	+	6	23	C.
5	+	7	24	C.
6	+	7	25	C. P.
7	+	6	21	C. P.
8	+	6	22	C. P.
9	+	6	22	C. P.
10	—	6	24	C.
11	+	6	24	C. P.
12	—	5	23	C.
13	+	5	23	C.
14	+	5	24	C. P.
15	+	5	24	C.
16	—	5	21	C.
17	+	5	23	C. P.
18	+	5	24	C. P.
19	+	5	24	C. P.
20	+	5	25	C.
21	+	5	25	C. P.
22	+	4.5	24	C. P.
23	+	4.5	24	C.
24	—	4.5	25	C.
25	—	4.5	21	C.
26	+	4.5	24	C.
27	+	4.5	24	C. P.
28	+	3.5	18	C.
29	—	4	21	C.
30	—	4	21	C.
31	—	4	21	C.
32	+	4	24	C.
33	+	4	24	C.
34	+	5	24	C. P.
35	+	4.5	23	C. P.
36	—	4.5	24	C.
37*	+	1	9	Positive again.
		2	15	Positive again. P.
38	+	3.5	25	C. P.
39	+	3.5	24	C. P.
40	—	4	21	C.
41	—	3	24	C.
42	+	3	21	C. P.

C. = stools cleared. P. = patient improved.

* All patients except No. 37 received 5 gm. carbarsone orally in 10 days; No. 37 received two such courses of treatment in 2 months.

In the ordinary case of chronic amebiasis with relatively mild symptoms, we have found that a total of 5 gm. of carbarsone, administered orally at the rate of 0.25 gm., twice daily for 10 days, is sufficient to clear the stools and to bring about clinical improvement. In severe infections this course of treatment may have to be repeated and in severe diarrhea it should be supplemented with carbarsone retention enemata (2 gm. carbarsone in 100 cc. of 1 per cent sodium bicarbonate solution), in order to achieve a satisfactory result.

No symptoms of arsenic toxicity were noted in any of these patients. Five patients, who received carbarsone purified by a different method from that employed in other lots of the drug which we used, gave evidence of local gastric irritation. This disappeared promptly, and was not observed subsequently on continuing treatment with carbarsone purified by the original method.

Conclusions. Our findings generally confirm those reported by Reed.¹ All but 1 of a group of 42 cases of amebiasis observed for 3 or more months after oral treatment with carbarsone were successfully cleared of *Entamoeba histolytica* (as far as careful stool examinations could reveal), without toxic effect and without hospitalization. It is our opinion that carbarsone offers a relatively nontoxic, satisfactory and cheap means of inaugurating therapy in amebiasis. It seems to be quite as effective as emetin, and is to be preferred as an initial therapeutic agent, because of the definite evidence of pathologic damage from emetin in the doses necessary for clinical effectiveness.² Acetarsone and chiniofon do not show as satisfactory an effect in amebiasis as we have found for carbarsone. In severe cases of amebiasis the recommended dosage of carbarsone (5 gm. in 10 days) may not be enough. Repetition of the course of therapy, supplemented with carbarsone retention enemata, is then indicated. Only after this would one seem to be justified in incurring the risks involved in emetin therapy.

BIBLIOGRAPHY.

1. Reed, A. C., Anderson, H. H., David, N. A., and Leake, C. D.: J. Am. Med. Assn., 1932, 98, 189.
2. Anderson, H. H., and Leake, C. D.: Am. J. Trop. Med., 1930, 10, 249. Rinehart, J. F., and Anderson, H. H.: Arch. Path., 1931, 11, 546

REVIEWS.

A TEXTBOOK OF HUMAN PHYSIOLOGY. By AUGUST KROGH, PH.D., LL.D., Professor of Zoöphysiology in Copenhagen University, Copenhagen. Revised and edited by KATHERINE R. DRINKER, A.B., M.D., formerly Research Assistant in Applied Physiology, Harvard Medical School, Boston. Pp. 233; 108 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$2.75.

THIS English translation of the author's book should prove a useful presentation of the elements of physiology. The facts are presented with a simple clarity worthy of a great master. Dr. Katherine Drinker in translating it has also added many useful, clear diagrams. The sections on circulation and respiration and the ideas of quantitative anatomy therein introduced make these sections particularly outstanding. Throughout the book there are few inaccuracies, though perhaps the treatment of the nervous system is the weakest part.

The Danish edition was prepared for school children of 16 to 18 years of age and for such students the book appears ideal. The English edition has been designed for the use of college students and one can only comment that if this is the kind of study that the college students carry on in American universities, it is a serious reflection on the standards of the colleges and confirms the criticisms that American colleges carry on too much superficial and elementary teaching. H. B.

THE HISTORY OF MEDICINE. By BERNARD DAWSON, M.D. (LOND.), F.R.C.S. (ENG.). Pp. 160; 31 illustrations. London: H. K. Lewis & Co., Ltd., 1931. Price, 7s. 6d.

AN evaluation of a volume that covers such a large field in such a short space is scarcely less difficult than its original composition. In order to avoid a mere cataloguing of facts certain items must necessarily be given more than their proper space, while others which may happen to appeal to the reviewer more than to the writer are properly entirely omitted. Perhaps the fact that these 7 lectures have proven profitable and entertaining for the junior medical students for whom they were prepared is sufficient guarantee of the value of the work to others. With such thoughts in mind, however, we question the value of such a book as compared to others of twice the cost and three times the size, that have mostly original instead of borrowed illustrations. All the more need too for a bibliography to help those who wish to read further in the matter. E. K.

ALLERGY and APPLIED IMMUNOLOGY. A Handbook for Physician and Patient, on Asthma, Hay Fever, Urticaria, Eczema, Migraine and Kindred Manifestations of Allergy. By WARREN T. VAUGHAN, M.D. Pp. 359; 21 illustrations and numerous tables. St. Louis: The C. V. Mosby Company, 1931. Price, \$4.50.

THERE are few conditions in which the *intelligent* coöperation of the patient is so essential for successful treatment as in the manifestations of

allergy. Physicians working in this field will therefore welcome this book for the better training of their patients. The general practitioner, also, will find an adequate statement of our present practical knowledge of allergy, as well as numerous references as a guide to further reading. The author brings to his task not only a thorough mastery of his subject, but also a delightfully clear and vivid literary style. R. K.

PAYING YOUR SICKNESS BILLS. By MICHAEL M. DAVIS. Pp. 276. Chicago: University of Chicago Press, 1931. Price, \$2.50.

AN interesting analysis of a complicated problem: the unevenness of the burden of sickness as it affects individuals, the factors which enter into the increasing costs of medical care, the attempts which have thus far been made to solve the problem. The author concludes that the solution lies fundamentally in the distribution of the financial burden either by taxation or by insurance. Physicians and laymen will find here not only food for thought but a guide for action. R. K.

CLINICAL ALLERGY. ASTHMA AND HAY FEVER. By FRANCIS M. RACKEMANN, M.D., Physician to the Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Pp. 617; 29 illustrations. New York: The Macmillan Company, 1931.

THE author states that the objects of this book are to digest the enormous mass of literature that has accumulated on this subject and by means of these sources, and particularly from personal experience, to define the present-day conception of the mechanism of asthma, hay fever and allied disorders and to discuss methods of diagnosis and treatment. He has succeeded admirably in producing a book which the general practitioner and the student will find complete, authoritative and readable. Special workers in the field will appreciate the extensive bibliography. R. K.

GYNECOLOGIC ROENTGENOLOGY. By JULIUS JARCHO, M.D., F.A.C.S., Attending Gynecologist and Obstetrician, Sydenham Hospital, New York. VOL. 13. ANNALS OF ROENTGENOLOGY. Edited by JAMES T. CASE, M.D., Professor of Roentgenology, Northwestern University Medical College, Chicago. Pp. 571; 273 illustrations, 5 colored plates. New York: Paul B. Hoeber, Inc., 1931. Price, \$20.00.

IN this monograph the author discusses the roentgenologic methods of diagnosis with the aid of pneumoperitoneum and iodized oil injections of the uterus and tubes. Ordinary roentgenology has little use in gynecology, being limited, according to the author, to the diagnosis of calcified fibroids, in which condition roentgenologic therapy is contraindicated.

The author discusses at length both pneumoperitoneum and uterosalpingography. The technique of both methods is detailed, not only as to the induction, which is of value to the gynecologist, but, as well, the roentgenologic details as to position, exposure and interpretation of the resulting picture. The author's experience with uterosalpingography has evidently been extensive. To emphasize certain points in technique and diagnosis he has introduced many pertinent case histories. A short section on radiation therapy gives in a concise, clear manner the major

points in generally accepted present-day technique. The book is profusely illustrated with excellent reproductions of appropriate roentgenograms and a number of color plates. It is in every sense an atlas of the subject. The literature has been widely searched and liberally quoted, and a large bibliography is appended, following which is an authors' name index.

While the author suggests that the volume is intended as a guide for roentgenologists assisting in such diagnostic methods, it should also be of unusual value to gynecologists as a very full exposition of the value of roentgenology in gynecologic diagnosis and therapy.

P. W.

APPROVED LABORATORY TECHNIQUE. Prepared under the Auspices of The American Society of Clinical Pathologists. By JOHN A. KOLMER, M.D., Dr.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania, and FRED BOERNER, V.M.D., Associate Professor of Bacteriology, Graduate School of Medicine, University of Pennsylvania, Assisted by C. ZENT GABER, A.B., M.D., Associate in Pathology, Peking Union Medical College, and Committees of The American Society of Clinical Pathologists. Pp. 663; 300 illustrations, 11 plates. New York: D. Appleton & Co., 1931. Price, \$7.50.

EVEN with the great number of books on laboratory technique that have recently flooded the market, this one should be welcomed not only on account of its intrinsic merits but on account of the official sanction that it received from The American Society of Clinical Pathologists. With the many and continuing additions to laboratory methods useful in clinical medicine, it has been inevitable both that the standards of technical performance should suffer and that the clinician often should not have sufficient knowledge to make maximum use of laboratory helps. Emphasis on the indispensability of accurate and reliable apparatus and reagents, and inclusion of methods used by practising veterinarians are noteworthy items in this book. It is richly and intelligently illustrated; however, the colors, especially of erythrocytes, are disappointing. Many would not agree that the exact source of platelets is as yet unknown (p. 95); "Reticulated erythrocytes" (pp. 92 and 93) is an obsolete term. Terry's quick surface staining biopsy method is not found. A more serious criticism is the omission of original references, which greatly restricts the potential value of this otherwise excellent book.

E. K.

THE MONGOL IN OUR MIDST. By F. G. CROOKSHANK, M.D., F.R.C.P. Pp. 539; illustrated. Third edition greatly enlarged and entirely rewritten. London: Kegan Paul, Trench Trubner & Co., Ltd., 1931. Price, 21s. net.

DOUBTLESS many will remember a small volume of the Today and Tomorrow series that caused amusement several years ago by the comparison of 3 main human stocks, Caucasian, Mongol and Negro, to the chimpanzee, orang-utang and gorilla. This has now reappeared, much enlarged and more fully documented, in a form that enables the author to put forward adequately the ideas that he has held for many years. Whether or not readers are convinced by his argument—and I doubt if many will be

—they at least will recognize the sincerity of the author and a measure of skill in maintaining a difficult thesis.

That the occurrence of Mongoloids in Caucasian populations is of anthropological as well as medical importance is a statement that will doubtless find considerable support. That the similarities which the author elicits among Mongols, mongoloids and orangs show a common ancestral origin for the three, closer for instance than Mongols and Caucasians, is a far different matter. The assumed relationship of negroes to gorillas and to Langdon-Down's Ethiopian idiot and of whites to chimpanzees and to microcephalics likewise remains unconvincing in spite of suggestive similarities of appearance and geographical distribution. The chimpanzee and the Sheikh of Fig. 9 seem remarkable for their dissimilarity; but one wonders why certain Irish types were not utilized.

Though the literary style adopted is better suited to entertain than to convince, the more serious minded reader will find plenty of pabulum set forth in the Appendices and extensive Bibliography. E. K.

MEDICAL MEN IN THE AMERICAN REVOLUTION, 1775-1783. The Army Medical Bulletin, No. 25. By LOUIS C. DUNCAN, LIEUT.-COLONEL, U. S. Army, Retired. Pp. 414; 53 illustrations. Carlisle Barracks, Pa.: Medical Field Service School, 1931.

For the interesting and important medical history of the Revolution, one has hitherto had to turn to James Thatcher's Journal, Surgeon-General Tilton's book on military hospitals, or such necessarily brief chapters as in Packard's "Medical History of the United States," or *ex parte* essays, such as John Morgan's "Vindication." Colonel Duncan's scholarly work not only remedies this deficiency but has combined with an authoritative statement a delightful story that once begun is apt to be read from cover to cover. Though the 52 illustrations are listed, by a curious oversight there are neither Index nor Table of Contents to the book. As the reviewer had to make his own Table he is passing it on to the reader: Chapter 1, Medicine and Surgery in the Colonies; Chapter 2, Making of the Army; Chapter 3, Siege of Boston; Chapter 4, The Canada Expedition; Chapter 5, The New York Campaign of 1776; Chapter 6, New Jersey Campaign; Chapter 7, Reorganization of the Army; Chapter 8, The Campaign for Philadelphia; Chapter 9, Burgoyne's Campaign; Chapter 10, 1778—Monmouth; Chapter 11, Medical Director Shippen; Chapter 12, The War in the South; Chapter 13, Medical Director John Cochran; Chapter 14, Yorktown; Chapter 15, The End; Appendix A, Losses; Appendix B, List of Medical Men who Took Part in the Revolution. If this sterling book is adequately known and appreciated, applications for copies to the Medical Field Service School at Carlisle should quickly exhaust the edition of 5000. If so, let us hope that a new edition with these omissions rectified will be made available.

E. K.

THE HARVEY LECTURES, 1930-1931, SERIES 26. Pp. 186; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$4.00.

THE contents of this volume are of interest not only in maintaining the high standard of presentation set by previous volumes but also as exhibiting both the changes in point of view as to well-known conditions and the emergence, often so gradual as to be almost unnoticeable, of new problems of medical importance. The 8 lectures in this volume are: The Female Sex Hormone, by R. T. Frank; Mass Action in Cerebral Function by K. S.

Lashley; Sinanthropus—Peking Man: Its Discovery and Significance by G. Elliot Smith; Psychoanalysis and Medicine by Franz Alexander; Possible Immunologic Reactions in Plants by E. M. East; The Coronary Artery in Health and Disease by James B. Herrick; Cold as an Agent in Physiologic Analysis by Sir William Hardy; Tissue Resistance and Immunity by Frederick P. Gay. While each reader will have his own preferences and the difficulties of condensing large topics into small space are recognized, the Reviewer would especially recommend the lectures of Elliot Smith, Herrick and Hardy. E. K.

THE WHITE HOUSE CONFERENCE PUBLICATIONS ON CHILD HEALTH AND PROTECTION. New York: The Century Company, 1932. *I. Health Protection for the Preschool Child.* By GEORGE TRUMAN PALMER, Dr. P.H., Chairman, Subcommittee on Statistics, MAHEW DERRYBERRY, Research Assistant, and PHILIP VAN INGEN, M.D., Chairman, Committee on Medical Care for Children. Pp. 275; 50 charts and numerous tables. 1931. Price, \$2.50. *II. Body Mechanics: Education and Mechanics.* Report of the Subcommittee on Orthopedics and Body Mechanics. By ROBERT B. OSGOOD, M.D., Chairman. Pp. 166; illustrated. Price, \$1.50. *III. Psychology and Psychiatry in Pediatrics: The Problem.* Report of the Subcommittee on Psychology and Psychiatry. By BRONSON CROTHERS, M.D., Chairman. Pp. 146. Price, \$1.50.

I. "This report undertakes to answer the question: To what extent is the health of the children in the United States who are the nucleus of the next generation being protected? The report is based on house-to-house inquiries made by representatives of nearly 1000 different local organizations, reaching 146,000 children in three-fourths of all cities of over 50,000 population and 37,000 children living in the rural areas of 42 states. The result is the most complete and graphic picture of how preventive medical and dental services are being applied to the preschool child which has yet been presented. The book is an invaluable addition to the literature of the preschool child. It includes an introductory statement regarding the present status of preventive medical and dental measures, a discussion of the findings of the survey, a series of reference tables showing in detail the survey findings in each area studied, and a discussion and explanation of the administration of the survey and the computation of the data collected."

II. "Body mechanics is defined . . . as 'the mechanical correlation of the various systems of the body with special reference to the skeletal, muscular and visceral systems.' There is positive evidence to prove that not less than two-thirds of the young children of the United States exhibit faulty body mechanics, and that this condition is likely to continue into adult life. The evidence gathered shows that improvement in body mechanics is associated with improvement in health and efficiency. An important distinction is made in the report between training in the principles of good body mechanics and training in various physical exercises."

III. "This report considers the important question, Should the medical practitioner attempt to give advice when difficulties threaten the satisfactory development of personality in a child under his care? Although the report does not urge all doctors to attempt to become expert in the fields of psychology and psychiatry, it states the opinion that adequate physical care of the child cannot be given without attention to whatever intellectual and emotional difficulties may be present, and concludes that when trouble arises and the individual child is in distress a well-informed and alert physician is the obvious adviser."

TRAITEMENT DE LA TUBERCULOSE PAR LA SANOCRYSIN. By KNUD SECHER, Médecin-Chef à l'Hôpital de Bispebjerg, Copenhague. Pp. 110; 21 illustrations. Copenhagen: Levin and Munksgaard, 1932.

SANOCRYSIN is one of a number of gold preparations employed in therapy of tuberculosis. The first part of the book briefly discusses the chemotherapeutic action of gold in experimentally produced tuberculosis as studied notably by Möllgaard. Different chapters discuss the following aspects: The method of administration and observation of patient; untoward reactions; indications and contraindications; use of gold in different forms of tuberculosis, especially pulmonary tuberculosis; a table of dosage and analysis of results. Excellent results are reported in therapy of medical tuberculosis. The book is a good brief presentation of the status of gold therapy. A number of references are given. Doses above 150 mg. of gold as advocated by the author are now no longer employed in many clinics on account of severe reactions. J. K.

A TEXTBOOK OF MEDICINE FOR NURSES. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., M.R.C.P., Senior Assistant Physician and Cardiologist, Royal Southern Hospital, Liverpool, etc. With a Foreword by Miss E. M. MUSSON, C.B.E., R.R.C., Chairman, General Nursing Council for England and Wales. Pp. 439; 38 illustrations. New York: Oxford University Press, 1931.

It is the author's object to give nurses a book that will be as practically helpful as possible, one that she may refer to as she cares for the patient and so add constantly to her fund of scientific knowledge.

In a clear, compact manner this text describes most of the problems in medical nursing, that a nurse needs to enable her to give the intelligent and satisfactory care, that is such a welcome help to the physician and comfort to the patient.

The chapters on Bacteriology and Therapeutics include only the essential elements that relate directly to nursing practice.

Special emphasis is given to the medical treatment and nursing care of all diseases discussed. An Appendix describes clearly the common technical procedures used. A Glossary, an Index and a Summary complete the book.

No review could adequately describe the wealth of material, the valuable illustrations and diagrams, some of which are colored, that are found in this book, nor give any hint of the beautiful style in which it is written. Aside from its value as a textbook that could be used with satisfaction anywhere this book is a fine piece of literature.

M. S.

BLOOD SUGAR IN NORMAL AND SICK CHILDREN. By ELISABETH SVENSGAARD. Pp. 245; illustrated. Copenhagen: Levin & Munksgaard, 1931.

In this monograph, translated into English from Danish, the author reviews the literature and gives her own data on fasting blood sugar values, blood sugar curves after ingested glucose and the effect of repeated glucose tests in the same individual. Data are given on 11 normal newborn infants, 26 normal infants from 15 days to 1 year, 22 normal children from 1 to 13 years of age, 5 children with celiac disease, 5 with chronic dyspepsia, 4 cretins, 5 children with eczema, 5 with rickets and 6 with tetany.

Findings of especial interest were the wide physiologic fluctuations in blood sugar curves after ingestion of glucose in infants on different days, and the very slight rise in the blood sugar after glucose feeding in celiac disease.

Noteworthy features of the work are the completeness of the protocols, and the large number of blood sugar samples taken in each curve.

I. Z.

THE BLACK DEATH AND MEN OF LEARNING. By ANNA MONTGOMERY CAMPBELL, Assistant Professor of History, New Jersey College for Women. Pp. 210. New York: Columbia University Press, 1931.

This is the first book of a series to be published under the auspices of the History of Science with the aid of an appropriation of the Carnegie Corporation to "assist in publishing important contributions to knowledge." Dealing with the greatest catastrophe that has befallen mankind in historic times, it tells a tale that is not only of absorbing interest to those who like to consider the present in the light of the past, but is also of scholarly value concerning the effect of the black death on the intellectual classes, the universities and science in general. The plague tractates, so productively studied by Sudhoff, with their revelation of contemporary views on the cause and nature of the disease and the accepted methods of protection, prevention and treatment, are first outlined. Later chapters portray in a well-documented but readable fashion the damage done by the pestilence to medicine, law, theology, politics and the sciences, both in the university and in extracollegiate activities. A 14-page bibliography, in addition to the copious footnotes, paves a broad approach for those who wish to go further.

E. K.

MEMORIE E COMUNICAZIONI SCIENTIFICHE (1894-1930). By PROF. CESARE SERONO, Dottore in Medicina ed in Chimica, Docente di Chimica e Microscopia Clinica nella R. Università di Roma. Pp. 701. Rome: Istituto Nazionale Medico Farmacologico Sersono, 1931.

THE book is a collection of scientific investigations previously published in various journals. The collection represents 40 years of the author's scientific activity and was published on the occasion of the twenty-fifth anniversary of the foundation of his institute.

The articles deal mostly with biologic chemistry, more and more leaning to the field of therapeutics.

Notable among these are studies on cholesterol and lecithin first introduced in human therapy by the author in 1897; studies on the physiologic and therapeutic action of lipoids, with special reference to cholesterol and lecithin (1911); researches on the various digestive ferments, their physiology and preparation in liquid form; studies on the therapeutic action of magnesium and calcium and their synergetic action, and finally (1923) researches on the action and preparation of insulin.

There are also several articles of interest to the clinical pathologist concerning mostly quantitative urinalysis.

The collection is preceded by a brief autobiographic sketch, and closes with a stimulating and somewhat prophetic article on life and radiation.

M. S.

MEDICINE IN VIRGINIA IN THE EIGHTEENTH CENTURY. By WYNDHAM B. BLANTON. Pp. 449; illustrated. Richmond, Va.: Garrett & Massie, Inc., 1931. Price, \$7.50.

To the author's former book, *Virginia Medicine in the Seventeenth Century* (AM. J. MED. SCI., 1930, 180, 715), is now added this larger work covering a period when the Old Dominion was not only in the heyday of her glory, but was *facile princeps* in intellect, wealth and prominence on this continent. A century which put the colonies well on the road to prosperity and developed a galaxy of brilliant minds relatively unequalled at that period or since was bound to have its interesting medical side. This the author has captured for us both in detail and in spirit. Though quacks were all too common, as indeed they always have been in this gullible land, men of high standards and ability were numerous in the profession and the habit of going abroad for one's education was in full swing. Even those who followed the apprentice system carried it out so thoroughly that much more of the available knowledge of the time was acquired by the intelligent student than is possible today.

The author, well versed in his subject, by correlating Virginia medicine with that of Europe and the other colonies, greatly widens the interest of his work to the reader. In the 18 chapters, not only are medicine, surgery and obstetrics depicted in some detail, but the related subjects of pharmacy, dentistry, nursing and botany receive understanding treatment. Especially interesting is the chapter on Jefferson and William Byrd of Westover, as examples of eighteenth century useful amateur scientists in medicine, while the chapter on Washington's last illness is of peculiar appropriateness at this time. Biographies of physicians in various Virginia towns and counties, while of more restricted interest, add to the value of the book as an historical record. The Historical Committee of the Medical Society of Virginia, of which the author is a member, is to be heartily congratulated on this concrete example of their activities. E. K.

LABORATORY DIAGNOSIS. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, and HAROLD D. HASKINS, M.D., Professor of Biochemistry, University of Oregon, School of Medicine. Pp. 475; 21 figures and 6 colored plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$5.00.

AN outgrowth of the outline used at the University of Oregon in teaching clinical pathology, this book attempts somewhat more than the usual manual of laboratory diagnosis. The usual description of methods, which occupies the latter half of the book, is preceded by 9 chapters on disorders of the various parts of the body that may best be investigated by laboratory methods. Thus in Chapter V (18 pages on Disorders of the Central Nervous System), the routine résumé in black-face type of essential points in anatomy, physiology and biochemistry is followed by a statement of indications for examination of the cerebrospinal fluid and several pages of interpretations of findings. A discussion of the colloidal gold test is followed by an outline of the systematic laboratory investigation of coma. This mode of treatment unavoidably leads to more or less repetition, which at times is *verbatim* (cp. erythrocytic diameters, on pages 192 and 375). Also while it undoubtedly offers in convenient form many considerations not included in the conventional laboratory manual, it is problematic whether many of these should not be left for more complete treatment elsewhere. The book is beautifully prepared and its statements accurate; it gives good value for the price charged. E. K.

INTERNATIONAL STUDIES ON THE RELATION BETWEEN THE PRIVATE AND OFFICIAL PRACTICE OF MEDICINE WITH SPECIAL REFERENCE TO THE PREVENTION OF DISEASE. Conducted for the Milbank Memorial Fund by SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. London: George Allen & Unwin, Ltd. Baltimore: Williams & Wilkins Company, 1931. Vol. I contains The Netherlands, Denmark, Sweden, Norway, Germany and Austria. Pp. 248. Vol. II contains Belgium, France, Italy, Jugoslavia, Hungary, Poland, Czecho-Slovakia. Pp. 249. Vol. III contains England and Wales, Scotland and Ireland. Pp. 558. MEDICINE AND THE STATE: THE RELATION BETWEEN THE PRIVATE AND OFFICIAL PRACTICE OF MEDICINE WITH SPECIAL REFERENCE TO PUBLIC HEALTH. With a Foreword by WILLIAM H. WELCH, M.D., LL.D., Pp. 300.

THE reviewer draws freely on Foreword and Preface: One of the major problems in public health administration is that of ascertaining the proper sphere of the private physician in the field of public health. During the past 7 years the Directors of the Milbank Memorial Fund have had occasion to consider this problem very seriously, in connection with the opposition of some members of the medical profession to certain phases of public health work inaugurated by the Fund. Finding few precedents in the United States to guide them, the Directors decided to arrange for an international investigation to throw light on the relationship between the fields of activity of private physicians and of physicians and laymen engaged in public health work. Hitherto most countries have evolved measures only as each pressing need has emerged. The different countries have not learned adequately from each other. To shed light on these questions a survey was conducted for the Fund by Sir Arthur Newsholme, M.D., K.C.B., former chief medical officer of the Local Government Board of England and Wales, and lecturer on public health administration, School of Hygiene and Public Health, Johns Hopkins University. The material gathered is presented in the first three volumes. The author points out that the observations have an additional value in that they were all made by the same individual and are therefore comparable. The specific medical problems which figure chiefly in the report are the methods of medical attendance on the poor, the provision of hospital treatment and consultative facilities for the sick, the medical phase of sickness insurance and the special problems of maternity and child welfare work, of school medical work and of work for the treatment and prevention of tuberculosis and venereal diseases. The fourth and concluding volume, *Medicine and the State*, summarizing the subjects as illustrated in the countries, surveyed, and presenting the author's conclusions and suggestions for action, is particularly recommended to all readers. These volumes constitute a contribution of the first importance in the field of social medicine. R. K.

NURSING IN NERVOUS DISEASES. By JAMES W. McCONNELL, M.D., Neurologist to the Philadelphia General Hospital; Associate Professor of Neurology, Graduate School of Medicine, University of Pennsylvania. Pp. 153; 24 illustrations. Philadelphia: F. A. Davis Company, 1932. Price, \$1.50.

THIS book admirably fulfills its purpose to make "life easier for both the student nurse and the patient suffering from organic nervous disease." The many illustrations are aptly chosen and each chapter ends with a list of pertinent review questions. Throughout, the utmost clarity is shown, but one regrets the narrow confines of the subject matter.

The important subjects discussed are: nervous system, nomenclature,

unconsciousness, apoplexy, epilepsy, diseases of the spinal cord, tabes dorsalis, poliomyelitis, neuritis, paralysis agitans, chorea, neuroses and psychoses.

Other useful subjects would be drunkenness, narcotic poisoning, heat prostration, tube feeding and even artificial respiration. The inclusion of nursing in mental diseases would not be difficult, and, since the same methods are frequently employed, not inappropriate.

As the book stands, it pertains too definitely to nursing in the nervous wards of the Philadelphia General Hospital, whereas, it should be worthy of a much larger field.

N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Internal Medicine. By various contributors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1316; 37 illustrations. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

Functional Disorders of the Large Intestine and Their Treatment. By JACOB BUCKSTEIN, M.D., Instructor in Gastrointestinal Roentgenology, Cornell University Medical College, etc. Pp. 223; 60 illustrations and 40 reproductions of radiographs. New York: Harper & Brothers, 1932. Price, \$3.00.

The Failing Heart of Middle Life. By ALBERT S. HYMAN, A.B., M.D., F.A.C.P., Cardiologist, Beth David and Manhattan General Hospitals, etc., and AARON E. PARSONNET, M.D., C.M., F.A.C.P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, etc. With a Preface by DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. Pp. 538; 166 illustrations, some in colors. Philadelphia: F. A. Davis Company, 1932. Price, \$5.00.

The Nature of Human Conflicts. By A. R. LURIA, Professor of Psychology at the Academy of Communistic Education; Research Associate, State Institute of Experimental Psychology, Moscow. Translated from the Russian and Edited by W. HORSLEY GANTT, Phipps Psychiatric Clinic, Johns Hopkins University, etc. With a Foreword by ADOLF MEYER, Professor of Psychiatry, Johns Hopkins University. Pp. 431; 133 figures. New York: Liveright, Inc., 1932. Price, \$4.00.

Your Teeth and Their Care. By CARL W. ADAMS, D.D.S., San Bernardino, Calif. Pp. 141; 30 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, \$1.25.

A sound elementary explanation in lay language of the structure of the teeth, their diseases and how they should be met.

Endocrine Medicine. Three Volumes and an Index Volume. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc., Member of Staff, St. Louis, City, Jewish, Baptist Sanitarium and Maternity Hospitals. With a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine. Vol. I. *General Considerations.* Pp. 460; 139 illustrations and 62 tables. Vol. II. *The Infantile and Juvenile Endocrinopathies.* Pp. 473; 109 illustrations and 25 tables. Vol. III. *The Adolescent and Adult Endocrinopathies.* Pp. 862; 255 illustrations and 26 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, \$35.00.

Hospitals and Child Health. A Publication of the White House Conference on Child Health and Protection. Reports of the Subcommittees on Hospitals and Dispensaries, CLIFFORD G. GRULEE, M.D., Chairman; Convalescent Care, ADRIAN V. S. LAMBERT, M.D., Chairman; Medical Social Service, IDA M. CANNON, R.N., Chairman. Pp. 279; illustrated with tables. New York: The Century Company, 1932. Price, \$2.50.

Pharmacology of the Medicinal Agents in Common Use. By STANLEY COULTER, PH.D., Sc.D. Pp. 254. Indianapolis: Eli Lilly & Co., 1932. Price, 50c.

"Heretofore there has been no comprehensive, small-size work on pharmacology. To meet this need Dr. Stanley Coulter, Dean Emeritus of the Purdue University School of Science, spent over three years in the preparation of a compact treatise on the pharmacology of the drugs now in common use by the medical profession. In this work he had the coöperation of members of the medical and research staffs of the Lilly Laboratories. The subjects are alphabetically arranged. Under each title there is a terse statement of the constituents of the drug, its physiologic action, dosage, and brief mention of its more important therapeutic uses. In no sense is this book intended to supplant the larger standard texts on pharmacology. On the other hand, it is the hope of its author and the publishers that the use of the pocket-size book will so intrigue the student in the subject that he will be led to closer studies of the great authorities on pharmacology."

The Psychological Effects of Menstruation. Nervous and Mental Disease Monograph Series No. 56. By MARY CHADWICK. Pp. 70. New York and Washington: Nervous and Mental Disease Publishing Company, 1932. Price, \$2.00.

Laboratory Service and the General Practitioner. By ARNOLD RENSHAW, M.D., B.S. (LOND.), D.P.H. (MANCH. and CAMB.), Director of the Laboratory of Applied Pathology and Preventive Medicine, Manchester, etc. With an Introduction by DAN MCKENZIE, M.D. (GLAS.), F.R.C.S.E. Pp. 267; 8 illustrations. New York: Oxford University Press, 1932. Price, \$2.50.

NEW EDITIONS.

Principles of Chemistry. By JOSEPH H. ROE, PH.D., Professor of Chemistry, George Washington University Medical School, etc. Pp. 427; 30 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.50.

A simple statement to meet the requirements of a 45-hour course in chemistry for nurses, with over 150 pages of exercises.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel, M.R.C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1493; 941 illustrations, 279 portraits. Sixteenth edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1932. Plain, \$7.00; Thumb Index, \$7.50.

A triumph of intelligent condensation, this new edition includes in a volume of convenient size more than 3000 new words, hundreds of which are "not defined in any other medical dictionary." Without laying any claims as an encyclopedia, it includes literally hundreds of indexed portraits, over a hundred tables, a 50-page therapeutic table, 941 illustrations with 105 in color, and a wealth of short biographic statements.

Bailey's Textbook of Histology. By ADOLPH ELWYN, A.M., Assistant Professor of Neurology, and OLIVER S. STRONG, A.M., PH.D., Professor of Neurology, with collaboration of others. Pp. 746; 529 illustrations. Eighth edition, revised and rewritten. Baltimore: Wm. Wood & Co., 1932. Price, \$5.50.

This is an especially valuable edition to own as it completes the changes only partly carried through in the previous edition. A new chapter on the Living Cell has been included and the attempt to correlate with function continued. Omission of the architectonics of the nervous system has necessitated a separate book composed of the "nervous" material of the seventh edition.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Viruses.—RIVERS (*Science*, 1932, 75, 654) writes that this is an age of extremes. There is a universal desire to express everything in the superlative tense; the largest ships in the world, the fastest automobiles, the smallest microorganisms. The fact that certain organisms are too small to be seen by the microscope lens adds importance and mystery to these objects. In the last few years there has been a very general increase in interest of scientists in these organisms and many unusual, odd and strange statements and conclusions have been made regarding the viruses. There is no reason to believe that all infectious diseases can be caused only by fungi, bacteria, spirochetes and protozoa or that all infectious agents must be viable. Some authors contend that in the virus group are included all infectious diseases whose etiologic agents are not known. This certainly cannot hold true for such disorders as smallpox, vaccinia, rabies and poliomyelitis; in other words, that these diseases are not caused by any known agent merely because such an agent is invisible or unable to be grown. On the contrary, writes the author, the viruses of many diseases are quite familiar to those who know. They can be distinguished from each other and from bacteria. Their presence can be ascertained easier and more readily than certain bacteria. They are recognized by the type of host attacked, by the clinical and pathologic pictures they induce and by the immunologic responses they excite. It is not necessary to see electricity nor to recognize it to control it, nor is it essential to see and grow every infectious agent. It has not been definitely proven, moreover, that an infectious agent must be viable; it is possible indeed that inanimate material may be capable of exciting disease just as it may be capable of exciting agglutination reactions when treated with a variety of proteins. It has not been proven and it seems quite unlikely to consider viruses merely as stages in bacterial life; even the existence of bacterial life cycles is doubtful. Other workers have become convinced that viruses are animate, yet they state that the size of the organisms causing foot-and-mouth disease is 8 to 12 μ .

The author, who of course is speaking only for himself, questions if it is possible "for an aggregate of so few protein molecules to be an organized living creature possessed of metabolic and reproductive powers comparable with those of minute bacteria." There is no reason to believe because viruses are smaller than bacteria that all of them are identical in size and shape, nor that they are of the same nature. "Some may be inanimate transmissible incitants of disease, others may be primitive forms of life unfamiliar to us, still others may be minute living organisms." It may be possible that viruses may be situated near the line that separates inanimate from living organisms. The author, furthermore, questions whether it is of supreme importance to know whether the viruses are living or merely the products of cellular perversion which are able to bring about similar perversion in other cells. The mere fact that it is not possible to see and cultivate the agents responsible for poliomyelitis, smallpox or yellow fever does not mean that it would be easier to handle these diseases from the preventive point of view if they could be observed and grown. The viruses of these diseases have been identified and kept bacteria-free. They can reproduce the disease in experimental animals, and protective serum can be obtained. Vaccination against virus diseases is more successful than in nearly any of the bacterial diseases. It is very doubtful indeed if the cultivation of the viruses on ordinary media would lead to obtaining agents superior to those already known, to combat many of the virus diseases. The chief difficulty in controlling these infections lies in the fact that they are spread usually from the upper respiratory tract. As the author rather facetiously suggests, it is essential to breathe and as yet no one has suggested a method to obtain uninfected air for the human beings living among their fellow men. To wait until viruses are seen and cultivated in a lifeless medium is merely to waste time. These diseases have been studied by methods other than the usual bacteriologic technique and a certain amount of success has attended these efforts.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Torsion of the Omentum.—MORRIS (*Arch. Surg.*, 1932, 24, 40) notes that Marchette reported the first case of torsion of the omentum in 1851. Corner and Pinches, in 1905, collected 54 cases. The present study brings the observed cases to a total of 217. The normal environment and anatomic arrangement of the great omentum are such as to favor rotation of this structure about its long axis, while the introduction of certain mechanical conditions and pathologic changes within and adjacent to it supply the immediate exciting causes of such rotation. It is clearly established that omental twists are capable of producing clinical symptoms of acute and chronic character, and that this condition therefore merits some consideration in the diagnosis of abdominal conditions. Variation in the intensity of degree of rotation

determines two basic clinical and anatomic types of torsion: (1) The complete, in which acute progressive symptoms and marked pathologic changes are dependent on complete permanent circulatory obstruction at the site of the twist; (2) the incomplete, which is characterized by vague, chronic recurring symptoms and mild pathologic changes in consequence of incomplete, partial or temporary obstruction, which permits repeated spontaneous restitution before pronounced organic changes develop. Diagnosis presents obvious difficulties as indicated by the fact that a correct pre-operative diagnosis was recorded in only 7.9 per cent of 217 cases. A statistical study of the series, however, emphasizes certain essential clinical manifestations and points of history, the recognition of which should enhance the precision of a pre-operative diagnosis. The deliberate fixation of the free margin of the omentum by suture to an adjacent structure may be the source of future complications, and its accidental inclusion during abdominal closure is to be avoided carefully.

Tumors of the Bile Ducts.—MARSHALL (*Surg., Gynec. and Obstet.*, 1932, 54, 6) finds that indications are that benign tumors of the bile ducts are extremely rare, that carcinoma is by far the most common neoplasm of the ducts, and that carcinoma of the bile ducts is more common in males than in females. Gall stones were present in 43 per cent of the cases on which this study was previously based. Obstructive jaundice has been found in most cases and may be extreme, fluctuating in severity or intermittent. The presence or absence of pain seems to be of little, if any, diagnostic significance. Typical biliary colic is not uncommon with tumors of the bile ducts unassociated with cholecystitis or cholelithiasis. The specific cause of obstructive jaundice is not easily diagnosed before operation. Positive diagnosis is rarely possible. Obstructive jaundice is usually a surgical problem, regardless of the type of lesion which causes the obstruction. Surgical treatment should have a favorable effect, because significant symptoms bring the patient to the physician early in the course of the disease and the tumor is small, slow growing and late to metastasize. Obstructive jaundice usually kills the patient, before the tumor itself has passed the stage of operability. Operations on tumors of the bile ducts carries a high mortality, because of the tendency to hemorrhage and the technical difficulties of operation on the biliary tract.

Skull Fracture Involving the Frontal Sinus.—GARDJIAN and SHAWAN (*Ann. Surg.*, 1932, 95, 27) report that incidence of frontal sinus fractures in a series of over 2600 cases of skull fracture is around 5 per cent. The majority of sinus fracture cases are asymptomatic. They should be confined to bed for a period of 8 to 10 days at least. They should not be permitted to blow the nose. Intranasal douches are contraindicated. The patient should be watched for infection in the sinus and suppuration within the cranial cavity. Compound fractures in this situation should be operated on as soon as the condition of the patient permits. The posterior wall of the sinus should be inspected. The great majority of frontal sinus fractures should be left alone. The results with conservative treatment are gratifying. The incidence of meningitis in this series was less than 1 per cent.

Sympathetic Ganglionectomy and Trunk Resection in Arthritis: Indications and Results.—HENDERSON and ADSON (*J. Bone and Joint Surg.*, 1932, 214, 47) state that it is apparent that there is a group of cases of chronic arthritis in which vasospastic phenomena are seen and are responsible for or aggravate the arthritic symptoms. Sympathetic ganglionectomy and trunk resection offer additional aid in the treatment of these patients, but extreme care should be exercised in the selection of cases. Sympathetic ganglionectomy and trunk resection are indicated for young persons who have vasomotor phenomena such as cold, wet, pale or cyanotic extremities, but whose arteries are patent, elastic and not occluded. The operation is not indicated in advanced cases in which there is marked ankylosis; neither is it indicated when the infectious process is still present. The operation affords the greatest amount of relief in the smaller joints of the extremities, fingers, hands, wrists, toes, feet and ankles. When there is involvement of the larger joints, such as the knees, hips, shoulders and spinal column, little is accomplished either in checking the disease or in ameliorating the symptoms.

The Use of Auscultatory Percussion for the Examination of Fractures.—LIPPMAN (*J. Bone and Joint Surg.*, 1932, 14, 118) writes that auscultatory percussion applied across fractures of the shaft of the femur, humerus and clavicle may be so interpreted as to indicate the presence of a complete fracture, the relative position of the fragments and, during the postoperative course, the development of bony union. The stethoscope bell and the percussing finger should be applied over bony prominences on either side of the fracture and the sound so elicited compared with that produced by the same procedure on the normal side. Sound alteration constitutes the criterion of the test. Pitch and quality changes result from free vibration of the separate fragments and accordingly signify complete fracture or incomplete union. Appreciable diminution in sound intensity indicates poor conduction and reflects absence of end-to-end contact. The application of the test is simple, rapid and entails no discomfort to the patient. The desired information is immediately obtainable. In the hospital it may be employed equally well with the patient on the orthopedic table, in traction apparatus, in bed or in a plaster cast, and is consequently applicable during, as well as following, reduction.

Prostate Operations: Prostatectomy vs. Resection.—DAVIS (*J. Am. Med. Assn.*, 1932, 97, 1674) states that early recognition and treatment of infection of the prostate is urged to prevent obstructions. Recognition of early obstructions and their correction by transurethral methods will lessen the number of advanced cases of prostatism. Prostatectomy, previously being the avenue offered, deterred many from seeking relief early before irreparable damage to the urinary tract and other organs had occurred. Resection (a term used for instrumental ablation) reduces the removal of the obstructing prostate to a minor surgical operation with the accuracy of a cystoscopic procedure and permits operation in the minutest detail under direct vision. Resection reduces the hospitalization to several days as compared to several weeks for prostatectomy with its economic considerations. In bars and con-

tractures, for accuracy and ease of operation, resection excels any method previously described. In these conditions there is no excuse for more radical measures. In the large hypertrophies that require one or more sections, with its freedom from mortality and discomfort to the patient, it should be the method of choice, as these conditions can be corrected without resorting to major surgical procedures. In inoperable carcinoma relief by resection is to be recommended over permanent suprapubic drainage.

Obstructions to the Ureter Produced by Aberrant Bloodvessels.—YOUNG (*Surg., Gynec. and Obst.*, 1932, 54, 27) writes that obstruction at or near the ureteropelvic juncture is not infrequently caused by vessels which run from the great vessels to the lower pole of the kidney. Two cases are reported in which these vessels caused an acute flexure, kinking and obstruction of the ureter, in 1 case bilateral and in the other unilateral. In the bilateral case the less affected kidney was operated upon first, and the aberrant vessels obstructing the ureter were clamped, divided and ligated. This was followed by a distinct postoperative reduction in the kidney function on this side. At the second operation the author carried out a new procedure (aplastic operation) by means of which it was possible not only to resect the very redundant pelvic sac, but also in closing it to draw the ureter away from the veins, so as to completely remove all possibility of obstruction. The result obtained in this case was completely satisfactory. The same procedure was carried out in the second case also with complete success. In the first case drainage of a huge hydronephrotic sac was kept up for over 1 month by means of a retained ureteral catheter passing out through the penile meatus. This resulted in an amazing restoration of this kidney, which was previously functionless, to practically normal function, so that it was possible to save this kidney and to carry out the conservative plastic of the pelvis with excellent results.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

The Treatment of Malignant Neutropenia With Pentose Nucleotids.—The stimulating effect of nucleic acid or its decomposition products on white blood cell formation has occasionally been reported in the literature. JACKSON, PARKER, RINEHART and TAYLOR (*J. Am. Med. Assn.*, 1931, 97, 1436) now publish the clinical results of treating 20 cases of profound leukopenia with intramuscular or intravenous injections of unbroken, pentose nucleotids ("nucleotid K 96," Eli Lilly Co.). In cases of acute illness 0.7 gm. of the nucleotid in 100 cc. of saline solu-

tion was injected intravenously, daily for 4 days; 0.7 gm. in 10 cc. of distilled water was also given intramuscularly on the same days and on each subsequent day until improvement was evident. Certain patients showed a sharp, temporary reaction to the intravenous injection. Seven of 13 patients with an apparent agranulocytic angina recovered under this treatment. In another patient the temperature and blood picture became normal but death intervened from pulmonary hemorrhage. Definite signs of clinical improvement appeared on the third or fourth day of the treatment. The blood picture improved between the fourth and seventh days, usually on the fifth. The total and differential blood cell count became normal 10 days after the treatment was started. Symptomatic improvement and healing of the ulcers occurred simultaneously with the improvement in the blood picture. All of 5 cases of malignant neutropenia associated with infection, treated similarly, recovered. In these 5 cases and the 8 with agranulocytic angina the charts of the temperatures and of the blood cell counts were practically identical. There is evidence that the nucleotid acted beneficially also in 2 cases of chronic benzene poisoning observed over a long period of time. In 1 case recovery appears certain. From the recovery of 14 out of 20 cases of malignant neutropenia treated with nucleotids, the authors conclude that these compounds react favorably on the inactive bone marrow of certain cases with this condition. They emphasize, however, that nucleotids are ineffective in leukemia and in sepsis without neutropenia and leukopenia.

Prostigmin, a New Peristaltic Agent.—ROTHSCHILD (*Med. Klin.*, 1932, 28, 365) reports the results of animal investigations upon the actions of a new synthetic alkaloid closely similar in constitution to physostigmin, which is introduced under the name of prostigmin. He finds that, when studied upon the isolated surviving intestine, prostigmin acts essentially as do physostigmin, pilocarpin and acetylcholin, increasing the muscular contractions of the intestine and raising the muscular tone as well as promoting increased peristalsis. It also effectively antagonizes the actions of atropin, adrenalin and papaverin. From these purely pharmacologic studies, it is apparent that the drug may be expected to be of use therapeutically as a substitute for physostigmin. Clinical studies on prostigmin by KOTTLORS (*Ibid.*, p. 366) show that in doses of 0.5 mg., injected subcutaneously, the drug increases intestinal peristalsis in a most effective manner. It not only increases the degree of intestinal contraction but it promotes the forward propulsion of the intestinal contents, probably more satisfactorily than does either physostigmin or pilocarpin. Doses of 0.5 mg. of prostigmin produce little or no disagreeable side actions, the only constant action observed being a slight slowing of the heart rate. It is effective also in man to overcome the action of atropin upon the intestinal tract. Its actions are well developed within about 15 minutes after its injection. These findings are established both by roentgenologic studies of the large intestine and from clinical observations in about 300 patients in whom prompt and effective emptying of the intestine, both of gas and of fecal contents, were secured. The patients included chiefly postpartum women and patients upon whom laparotomy had been performed. The effectiveness of the drug in promoting evacuation

is much increased if a small enema of from 20 to 50 cc. of glycerin be given. The author regards prostigmin as being preferable to physostigmin because of the absence of side actions and because of its production of increased physiologic motility of the intestine without the tendency to produce excessive contraction and cramps.

The Effect of Insulin on Gastric Secretion.—This problem is of special interest, both because of the frequently reduced or absent hydrochloric acid in the gastric secretion of diabetic patients and because of the use of insulin for the increase of appetite and gain of body weight. LURJE and ELIJIN (*Wien. klin. Wchnschr.*, 1932, 45, 492) studied the effect of 10 to 20 units of insulin on the gastric secretion in 22 cases in which 35 observations were made. In all of the cases with normal or hyperacidity there was an increase in the gastric acidity due to insulin. In cases with gastric anacidity insulin usually produced no change, but in some instances hydrochloric acid appeared following insulin therapy.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Milk Irradiated by Carbon Arc Lamp.—HESS and LEWIS (*J. Am. Med. Assn.*, 1932, 99, 647) activated pasteurized milk by means of carbon arc rays, and carefully controlled and measured the radiant energy. They found that exposure of 16 seconds was sufficient to render the milk antirachitic. A clinical test of this product in the prevention and cure of infantile rickets showed that it is a highly effective antirachitic agent which can be relied on. Less than 1 quart daily sufficed to protect even negro infants. The great advantage of using activated milk, both fluid and in the dry form, in the prophylaxis of rickets, is that this furnishes an automatic method of therapy and likewise provides calcium and phosphorus. Laboratory tests of this milk showed that it contained a comparatively small number of antirachitic units as judged by the standard rat assay. In view of the excellent clinical results it is evident that the established method of assay cannot be relied on to appraise the value of irradiated milk for infants. This discrepancy in standardization also was found to hold true for tests of milk from cows that had been fed irradiated yeast. The indications for various antirachitic agents is variable. The most outstanding are irradiated milk either fluid or dry, milk from yeast-fed cows, cod-liver oil, viosterol and irradiated yeast, and direct ultraviolet irradiation, and concentrates and combinations of these products. These measures differ not only in their specific virtue, but also in their applicability according to whether one is considering individuals or a community, whether the community is rural or urban, and at all events according to the cost of the preparation.

Studies in Status Lymphaticus and Its Relation to Anesthetic Deaths.
—KEMP (*Anæsth. and Analg.*, 1932, 11, 128) reviews clinical, physio-

logic and pathologic evidence to show that, in animals and individuals in whom enlarged thymus as well as hyperplastic mesenteric lymph glands were found at postmortem, there is definite evidence of a relatively deficient endocrine function. The glands that play the important part of being deficient are the adrenals and the thyroid group which contains the thyroid and the thymus. Pituitary and gonadal dysfunction play a less important part. He defines status lymphaticus as a relative or absolute endocrine insufficiency leading to a disturbed metabolism and an unbalanced autonomic nervous system, with the consequent liability to the sudden onset of cyanosis and shock and death from little or no apparent cause. As yet the only recognized features on postmortem are enlarged mesenteric lymphatic glands and usually a thymus that is larger than the average for the age and state of nutrition. The symptoms of this state are dyspnea, cyanotic attacks not of cardiac origin, intermittent suffocative spasms with or without fits of crying or temper, stridor, paroxysmal coughing or choking attacks, shock and collapse from seemingly insufficient cause. The dyspnea is due to an anoxemia from a sudden change in a blood stream which no longer is able to carry oxygen. This he attributes to the lack of adrenal hormone. The cyanotic attacks are attributed to the same cause. The suffocative spasms, the stridor or laryngismus stridulus he attributes to the preponderance of the parasympathetic or vagus division of the autonomic nervous system acting upon the musculature of the larynx and bronchi. He blames the same vagotonia for the paroxysmal coughing and choking attacks, and the shock, collapse and death are the end results of the disturbed metabolism and disturbed autonomic nervous system resulting from endocrine dysfunction.

The Schick Test in Infancy.—GREENGARD (*Arch. Ped.*, 1932, 49, 526) gave 584 infants periodic Schick tests. In all 1140 tests were done on these children. He found that the positive reactions according to age groups was in strict agreement with the mass of statistics accumulated relative to the incidence of the positive reaction in infancy. The transition from a negative to a positive reaction was demonstrated in 114 of these infants. This curve demonstrated the great variability in the duration of the passive immunity in infancy. A few of the infants showed the loss of immunity as early as the first to the third month of life. In some this immunity persisted past the first year of life and after 18 months in some cases. The greatest percentage of cases showing the loss of immunity as measured by the Schick test fell in the age group of 4 to 10 months. Comparative Schick tests were carried out on a group of 100 infants and their mothers. In this group a definite lack of agreement between the tests of the newborn and their mothers was found. Sixty per cent of the newborn infants of positive mothers gave negative reactions to the Schick test and in every instance in which a positive was obtained, the reaction of the infant was much less intense than that of the mother. All the infants of negative mothers reacted negatively. He found that the incidence of the positive Schick test in infancy varied from 17.6 per cent in the newborn period to 70 per cent at 1 year of age. Almost 80 per cent of the infants had lost their immunity by the end of the ninth month. While the positive Schick test is indicative of lack of specific immunity in the newborn, the negative Schick test

is of no significance in this age period since a large proportion of infants without antitoxic immunity show no reaction to intradermal toxin. This lack of sensitivity to intradermal diphtheria toxin is demonstrated by other types of skin irritants as well, and is due to a specific lack of reactivity of the skin of the newborn or a cutaneous energy.

Erythroblastic Anemia.—KOCH and SHAPIRO (*Am. J. Dis. Child.*, 1932, 44, 318) state that erythroblastic anemia should be considered as a definite disease entity. It is a grave and chronic anemia with familial and racial tendencies. Chronic infections, rickets and other nutritional disorders are of no etiological importance. The onset is in early infancy and is accompanied by splenomegaly and some degree of icteric discoloration of the skin. There may be progressive enlargement of the cranial and malar bones with associated mongoloid facies. Studies of the blood frequently reveal, besides the low hemoglobin and the erythroblastosis, a leukocytosis of varying degree and often an increase of myeloid or lymphoid cells. There is evidence of increased hemolysis in the high icteric index and positive indirect van den Bergh reactions, although the fragility of the red cells is not increased. The course is not altered by any of the recognized forms of hematopoietic stimulation. The benefit of a transfusion of blood is but temporary. Following splenectomy there is a marked and sustained increase in the circulating normoblasts. This is characteristic, but general improvement is not observed.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Chemical and Electrolytic Lesions of the Mouth Caused by Artificial Dentures.—LAIN (*Arch. Dermat. and Syph.*, 1932, 25, 21) discovered upon routine examination of the mouths of 45 consecutive adults wearing full-plate dentures that 42 per cent had either stomatitis or glossitis. Most of these cases were due to neglected oral hygiene, malocclusion or trauma caused by imperfect adaptation of the plates to the alveolar processes. In several cases, however, the pathology was attributable by a process of exclusion, to the porosity of the plates which contained free mercury sulphid and sulphur in one instance, and aluminum powder with a trace of zinc in another. Macroscopic and microscopic analysis of other offending plates showed undercuring with porosity. Another interesting group of 30 adults, whose mouths contained two or more metals of different potentialities, registered from 1 to 40 degrees of galvanic current on the microammeter. One case of a metallic upper

plate with amalgam fillings below registered a dangerously high degree of current. A large percentage of patients with two or more kinds of metallic dentures complained of symptoms, such as metallic taste, burning tongue and acute dental nerve sensations, or presented visible mucous lesions adjacent to or between metallic dentures. The author believes that these lesions are an expression of the irritation from galvanic discharges within the mouth, the saliva acting as an electrolyte.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Period of Conception.—OGINO (*Zentralb. f. Gynäk.*, 1932, 56, 721), of Japan, has been interested for several years in the relationship of the time of ovulation to the possibility of conception. In his present contribution, based on rather extensive clinical observations, he states that in 14 cases of pregnancy in which the day of conception was definitely known, that day was never after the period of ovulation in the menstrual cycle. In 5 fertile women observed during a period of 115 months there were 242 sexual contacts after the period of ovulation, *i. e.*, during the 11 days preceding the next expected menstrual period, without 1 instance of pregnancy. In 13 out of 14 pregnant women in whom the date of conception was known, intercourse had always occurred during the period of ovulation or within 3 days preceding it, since the spermatozoa may remain alive for 3 days in the female genitalia. In 1 patient the date of intercourse was 4 days before ovulation. He believes, therefore, that the time during which a woman may be impregnated is, as a rule, during a period of 8 days which occurs between the 12th and 19th day before the next menses. These 8 days represent a 5-day period of possible ovulation plus the 3 preceding days during which viable spermatozoa may be in the female genitalia. During the period of 20 to 24 days before the next menses (4 to 8 days before ovulation) conception is seldom possible while during the 11 days immediately preceding the menses (postovulation period) he definitely states that conception is impossible. From the practical standpoint the conception period may be figured from the last menstrual period. In the 28-day cycle this period would be from the 10th to 17th day after the beginning of the last period. When the cycle is longer or shorter than 28 days the period of conception will vary accordingly, being moved back in the longer type and forward in the shorter type. In cases where the menstrual cycle is irregular he has constructed formulas, thus: Beginning of conception period equals $10 +$ (minimal

cycle, 28 days). End of conception period equals $17+$ (maximal cycle, 28 days). The results of these formulas express the number of days after the last period. In estimating the cycles it is necessary to take at least 12 cycles to get an average for both maximal and minimal, as 3 or 4 cycles would not be sufficient. These formulas are practically of value only to those women whose variation is not over 10 days, since the greater the variation, the less the value of the formula. For instance, in women whose cycle varies from 26 to 36 days the beginning of the conception period would be $10+$ ($26 - 28$) or 8 days and the end of the conception period would be $17+$ ($36 - 28$) or 25 days after the beginning of the last period. If the next cycle would be of the minimal type menses would occur on the 27th day so that there would be only 1 day between the 25th and 27th when she would be absolutely sterile. If the next cycle were of the maximal type she would have 11 days before the onset of the following period when she would be sterile. This work is very interesting from the academic standpoint, but it is doubtful whether it will be of much practical value, as in general it would seem to be rather awkward to correlate sexual desire with mathematical formulas.

Fibroids and Ovarian Cysts Complicating Pregnancy.—According to LYNCH (*California and West. Med.*, 1931, 35, 415), when a patient who is very anxious to have children presents herself during the second or third month of pregnancy with a complicating uterine fibroid, unless the fibroid is cervical, there are four possible plans of treatment: (1) Hysterectomy, (2) induction of abortion with subsequent removal of the tumor, (3) myomectomy with or without removal of the fetus and (4) allow the woman to progress in her pregnancy and meet emergencies if they arise. After a thorough discussion of these four plans of treatment, he believes that, in general, patients without pedunculated tumors should be allowed to progress in the pregnancy if they possibly can. Nature very often overcomes difficulties that seem impregnable even to the obstetrician of widest experience, and many cases come to term. Most of the women who are seen at term with large fibroids in the fundus deliver quickly and spontaneously. If they do not deliver quickly the labor may be quite prolonged since fibroids are frequently a cause of inertia. When there is an indication for Cesarean section at term the question often arises whether it should be followed by hysterectomy or myomectomy. Hysterectomy is relatively safe, but if the patient is young it should be remembered that the fibroids often involute after delivery to such an extent as to seem to have disappeared. There is little difference of opinion as to the proper treatment of ovarian cysts discovered early in pregnancy, as they should be removed whatever their size, type or location. The fourth month of pregnancy is probably the time at which abortion is least likely to follow operation. In brief it may be stated that in dealing with fibroids complicating labor or pregnancy one must have an exceptional case if operation is required, while with ovarian tumors one must have an exceptional case if operation is not required. (The fact that about 14 per cent of all ovarian neoplasms are malignant, and that frequently malignancy cannot be recognized preoperatively, is a strong argument in favor of immediate operation in the latter group.—C. C. N.)

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

Eye Changes in Congenital Cardiac Defects With Polycythemia.—GINSBURG (*Klin. Monatsbl. f. Augenheilk.*, 1928, 81, 591) reports the eye findings in 3 cases of congenital stenosis of the pulmonary artery with secondary polycythemia. In the first patient, a child, aged 5 years, the erythrocytes numbered 6,500,000 per c.mm. and the hemoglobin percentage was 80. Ophthalmoscopic examination revealed hyperemic disks with sharp margins, dark-colored and somewhat dilated but not tortuous veins, with a suggestion of interrupted blood stream, normal arteries, and some grayness of the peripapillary regions. In the second patient, a girl, aged 20 years, the erythrocytes numbered 7,640,000 per c.mm. and the hemoglobin percentage was 85. The eyelids and conjunctivæ were cyanotic and the skin, conjunctival and scleral veins were dilated. The optic disks were bright red with clear margins, and the peripapillary and peripheral retina had a grayish-blue tint. The retinal veins were tortuous, cyanotic, dilated to about twice their normal size and showed a broad central light reflex. The blood stream in the veins appeared interrupted in spots. The arteries were somewhat broader and darker than normal, were tortuous and showed a broad light reflex. The finer twigs of the retinal vessels were definitely dilated and visible. In the third patient, a girl, aged 16 years, the erythrocytes numbered 9,800,000 per c.mm. and the hemoglobin percentage was 90. The conjunctivæ were markedly cyanotic and showed dilated veins, more on the right. The right iris showed many new-formed vessels. A massive hemorrhage in the vitreous prevented a view of the right fundus. Secondary glaucoma was present. In the left eye the disk was bright red with clear margins. The retinal veins were markedly dilated and tortuous, were of dark violet, almost black color, and showed localized dilatations. The arteries were not dilated but were darker than normal and markedly tortuous. The retinal vessels had broad light reflexes and the smallest vessels were dilated and tortuous. Histologic examination of the eyes of Case 3 showed the marked thickening and hyalinization of the walls of the dilated vessels in the iris, ciliary body, choroid and retina. In the left eye a large hemorrhagic infarct was present in the periphery of the retina. In the right eye many vessels showed also endothelial proliferation, with narrowing and frequently obliteration of the lumen. Numerous hemorrhages were present in the retina, between the retina and the choroid, and in the vitreous. The angle of the anterior chamber was obliterated. The author concludes that the changes seen in the retina in polycythemia vera and in congenital cardiac defects with secondary poly-

cythemia are essentially the same and that the ophthalmoscopic appearance of the vessels depends in both diseases on the increase of red cells with the resultant increased viscosity and specific gravity of the blood, slowing of the circulation and disturbance of the nutrition of the vessel walls. Histologic examination of the eyes in both diseases shows degeneration of the vessel walls with resultant hemorrhages. The degree and type of the cyanosis retinæ depends on the amount of increase in the red cells and not on the type of disease causing the increase. From his findings in these 3 cases the author believes that a light reflex is present on the retinal vessels whenever they push forward or elevate the internal limiting membrane of the retina. His histologic findings in the right eye of the third case support the view that hemorrhagic glaucoma is dependent on disease of the ocular vessels and on closure of the angle of the anterior chamber by inflammatory adhesion between the root of the iris and the posterior surface of the cornea. That this closure of the angle precedes the development of glaucoma is suggested by the finding of round-cell infiltration in the tissues at the iridocorneal angle in the left nonglaucomatous eye.

Ocular Manifestations in Cranial and Intracranial Injuries.—PRINGST (*South. Med. J.*, 1932, 25, 357) reports 2 rather unusual ocular complications of head injuries. Isolated paralysis of the superior oblique muscle of the left eye was observed in a boy, aged 11 years, following an injury which resulted in 3 linear fractures in the parieto-occipital area, 1 of which extended downward into the base. The paralysis cleared up in about 6 weeks. Right homonymous hemianopsia and left homonymous lower quadrant anopsia were found in a man, aged 48 years, who had noticed difficulty in seeing to the right immediately upon regaining consciousness after a fall on the face. The field defects were progressive. At operation a cyst containing blood-stained fluid was found deep in the substance of the occipital lobe below the calcarine fissure. Vision returned to normal after evacuation of the cyst. Hemianopsia reappeared with the refilling of the cyst and disappeared with a second emptying of the cyst. The author calls attention to the lateralizing value of a unilateral dilated pupil after head injuries. He does not believe that fundus changes appear early, though he states that it is "not unusual after 10 to 12 hours to find a general retinal edema and a slight engorgement of the veins." True choked disk is a rare symptom in fracture of the skull. Occasionally nystagmus is present, due to injury to the semicircular canals, the oculomotor center or tract, to the 4th ventricle, or to the medulla. Paralysis of an external eye muscle may occur immediately or, with delayed hemorrhage, 2 to 3 weeks after the injury. The 6th nerve is the most frequently injured. Paralysis of eye muscles usually recover in from 1 to 10 weeks. In anterior fractures of the skull extending into the optic foramen the optic nerve may be injured with resultant blindness and loss of pupillary reaction on the side of the lesion. The optic disk in such cases is normal at first, but in 2 or 3 weeks shows optic atrophy. In fractures of the middle fossa the chiasm may be injured with resultant bitemporal hemianopsia.

RADIOLOGY

UNDER THE CHARGE OF

ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,

CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Cleidocranial Dysostosis.—A case of cleidocranial dysostosis is reported by KLEMMER, SNOKE and COOPER (*Am. J. Roent. and Rad. Therap.*, 1931, 26, 710). The patient, a girl, aged 12 years, could readily approximate the deltoid eminences anteriorly, thereby decreasing the shoulder width to less than 6 inches. Her anterior and posterior fontanelles were about $\frac{1}{2}$ inch in diameter; the clavicles were absent except for bilateral stumps, each 2 inches in length and attached to the sternum; the supraspinous fossæ were absent, and the fingers and toes were short and tapering.

Roentgenologic Studies in Early Lobar Pneumonia.—It is generally conceded, says UDE (*Am. J. Roent. and Rad. Therap.*, 1930, 26, 691) that the demonstration of a triangular area of consolidation is frequently the earliest roentgenologic finding in lobar pneumonia. However, certain observers distinctly recognize "central" or "hilum" pneumonia and conceive it to be limited to the parahilar tissues without assuming the cone shape. On the other hand, Weill and Mouriguand, from a study of 350 cases, concluded that the shadow is usually triangular with its base always cortical. The author has studied 13 cases where the shadows in the anteroposterior view were of the "central" type, but in the lateral view it was found that the apparently "central" shadow was conical, posteriorly situated and had its base on the periphery of the lung. He feels, therefore, that lateral roentgenograms of so-called "hilum" or "central" pneumonia show that the term is a misnomer, that these medial shadows are in reality posterior cone-shaped consolidations, and that they may be best defined as "early posteromedial" consolidations.

Gastric Tumors.—A patient who gives a history of chronic dyspepsia and who has free hydrochloric acid in the gastric contents may, notwithstanding the latter finding, have cancer of the stomach. This patient, claims DWYER (*Radiology*, 1931, 18, 80), is just as deserving of a detailed study to determine or rule out cancer as is one who consults a physician on account of comparatively recent gastric symptoms. Among his series of patients 38 per cent had a history of dyspepsia for 10 years, and 70 per cent had free hydrochloric acid. A benign tumor of the stomach, although rare, may be the cause of an atypical gastric complaint, with anemia, loss of weight, diarrhea or weakness. The value of careful palpation of the stomach during roentgenoscopy cannot be emphasized too strongly; otherwise polypoid tumors are likely to escape discovery.

The Roentgen Ray in the Diagnosis and Prognosis of Upper Urinary Tract Infection.—In the roentgenologic study of the kidney **PLAGGE-MEYER** and **WELTMAN** (*Radiology*, 1932, 18, 23) regard roentgenoscopic pyelography as essential. By this method overfilling of the pelvis and consequent pain to the patient can be avoided. Obscure details can be studied better than in the pyelograms. Under vision the kidney can be palpated and its mobility and the relation of calculi, tumors, etc., can be noted.

Intravenous Urography.—One hundred and twenty-three consecutive intravenous urographic examinations have been made by **CUMMING** (*Radiology*, 1931, 18, 41). He has employed pyelognost, skiodan and uroselectan, and finds the last named to be most satisfactory. With all three drugs he has seen temporarily alarming reactions. He deplors a tendency among practitioners to an overenthusiasm for intravenous urography which is not shared by urologists. He feels that this method of diagnosis should not be practised by urologists and roentgenologists independently, and that general laboratories should not attempt to place lesions of the genitourinary tract by intravenous urography.

Ear Complications in Acute Craniocerebral Injuries.—Four hundred and seventy-six cases of aural bleeding or cerebrospinal fluid leakage are reported by **GURDJIAN** (*Radiology*, 1931, 18, 74). The right ear was affected in 36.5 per cent, the left in 41.3 per cent and both in 20.6 per cent of the cases. In more than 93 per cent a fracture somewhere in the skull was revealed by the Roentgen ray. Most common was a fracture line in the mastoid region extending toward the occipital bone. Many had fractures in the parietal bone extending down into the middle fossa. Others had fractures in the region of the foramen magnum. A certain number of frontal sinus fractures exhibited aural bleeding.

Treatment of Superficial Fungus Infections With the Long Wave Length Roentgen Rays (Grenz Rays).—**DORNE** and **WHITE** (*Radiology*, 1932, 18, 727) relate their experience with 22 cases additional to 30 previously reported, which were considered to be examples of superficial fungus infection and were treated with fractional doses of Grenz rays. With such dosage those infections due to yeast-like fungi responded quite uniformly, while those of hypomycetic origin showed very little improvement, if any.

Roentgen Ray Treatment of Keloidal and Hypertrophic Scars.—In the opinion of **SHERMAN** (*Radiology*, 1932, 18, 754) prognosis as to the result from treatment should be guarded in every case of keloid or scar, be it ever so recent, being particularly cautious as regards the syphilitic type, the tuberculous, erosions on the face, hard lesions and lesions in the dark-skinned races. The Roentgen ray should not be pushed to the point of producing telangiectasis. Probably the most important item in the treatment of these conditions is caution, fearlessness in calling on the plastic surgeon when he is needed, and especially caution in the prognosis, as it may save embarrassment later.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
DENVER, COLORADO.

The Acid Base Equilibrium of the Blood in Psychotic Patients With Special Reference to Affective Psychoses.—APPEL, FARR and HODES (*J. Nerv. and Ment. Dis.*, 1932, 75, 22), feeling that the usual blood chemistry determinations offer little that is helpful for understanding the neuroses and psychoses, present a study of 120 psychotic patients and 15 normal persons. In this study they show that the chemical measurements of the electrolytes and acid-base equilibrium in the blood serum by methods that have recently been developed offer little that is enlightening in regard to these conditions. They found that: (a) The total base content of the blood plasma in psychotic individuals is normal; (b) the blood chlorids in these same cases are also normal; (c) the carbon dioxide content of the plasma in their psychotic cases lies within normal limits except in those cases complicated by "new admission," toxic conditions, physical abnormalities or resistance to vena puncture; (d) the "acid residue" is increased in the involutional depressions.

Postoperative Result of a Chronic Right-sided Hematoma With Ipsilateral Pyramidal Tract Signs.—COHEN (*Arch. Neurol. and Psychiat.*, 1932, 27, 219) presents the case of a man, aged 30 years, in whom a headache developed a few days after a fall. Three weeks later dimness of vision and weakness ensued. Six weeks after the trauma he had choked disks; he fell backward on standing or walking. There were a right central facial weakness, increased knee jerks on the right, diminished abdominal reflexes and an equivocal right plantar response. The spinal fluid pressure was 440 mm. of water. Ventricular studies showed only a few cubic centimeters of fluid from each side. An exploration was performed on the left side and nothing was found. A week later ventriculogram showed a shift to the left of the ventricles. Ten days later an exploration of the right side revealed a chronic subdural hematoma, following the removal of which there was prompt recovery.

The Meaning of the Dream.—LONDON (*J. Nerv. and Ment. Dis.*, 1932, 75, 40) states that dreaming primarily is an outlet for our pent-up desires and ambitions. "In fact, it is a protector of sleep." But the symbolism of the dream in which sex symbolism plays an important rôle is of utmost significance. To say that sex is the only motive in dreams is to be ignorant and perverse. Many individuals remark that

they never dream. This is not so, for if it were not for the dream we would be unable to sleep. Thus persons who suffer from insomnia are the victims of conflicts between their instinctive forces and moral training; however, when these instinctive forces and moral forces are in accord successful dream work is formed and sleep is rendered more likely. The language of the dream is a picture code; it represents ideas by means of symbols. In dream life all experiences are pictorial or photographic and the images are stored in the psychovisual field of the occipital lobe. The image after reaching the retina travels by the visual fibers to the optic chiasm, then to the crus cerebri, to the primary optic centers and then by the optic radiations to the occipital lobe, where the photographic images are stored as memory. If for some reason or other the experiences are painful to our conscious part of the psyche, they are discarded from consciousness into the unconscious, the unconscious division being present in all sensory cells of the cerebrum.

Effects of Total Removal of Left Temporal Lobe in a Right-handed Person: Localization of Areas of Brain Concerned With Speech.—DANDY (*Arch. Neurol. and Psychiat.*, 1932, 27, 221) claims that the results of cerebral extirpations in human beings show that auditory speech is located in the parietal lobe, that visual speech is entirely distinct and separate anatomically from auditory speech, and that Broca's area occupies essentially the area described by Broca, except that it is possibly a little more posterior. To support these statements the author presents 3 cases: (a) A man, aged 21 years, in whom the entire left temporal lobe was removed. Four months after the operation there was no defect of speech that could be attributed to the extirpation of cerebral tissue, nor at any time did the patient show any auditory aphasia. (b) An individual in whom the entire left occipital lobe was resected, the supramarginal and supraangular gyri were included. The plane of the incision was vertical and slightly behind the postcentral gyrus. A month after the operative procedure the patient showed an absolute visual aphasia. He is unable to read a letter; he can write perfectly from dictation but cannot read anything he has written. He has no auditory aphasia. (c) A patient who had a constant series of Jacksonian convulsions beginning in the right side of the face. A small tumor together with a small zone of tissue was excised. The patient never recovered speech, so that he had a total motor aphasia but no sensory aphasia.

A Peculiar Type of Polyneuritis.—A FOREIGN LETTER (*J. Am. Med. Assn.*, 1932, 98, 246) states that Dr. TerBraak gives observations in 10 cases of polyneuritis that developed in Amsterdam, in women, during the space of 3 months, and characterized by: (1) Predilection for groups of muscles of the extremities and well delimited; (2) symmetry of the phenomena; (3) absence of objective disorders of sensibility; (4) abolition of the Achilles reflex and persistence of the patellar reflex. In 9 cases it was established with certainty that the women had, from 10 to 20 days before the onset of the disease, made use of the same or similar means of inducing abortion. Every other cause appeared to be excluded. A similarity between this group of cases, clinically homogeneous and of a special type, with other epidemic cases

described in the forepart of 1930 in the United States under the name of "ginger paralysis" and due to the use of an adulterated extract of Jamaica ginger was observable; there is a still greater similarity to the cases of polyneuritis formerly but not now so generally known, caused by creosote phosphate, a remedy formerly much recommended by charlatans for tuberculosis.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Influence of the Parenterally Introduced Aorta Wall Cell Constituents on Blood Pressure and Blood Gas.—SATO (*Japanese J. Exper. Med.*, 1931, 9, 509, 519, 527) discusses the above problem under three headings: I. Influence of the Endothelial Cell Constituents on Blood Gas. Cattle aorta endothelial cell emulsion was injected into the abdominal cavity of rabbits and the following changes in the blood gas content were observed. Doses of 0.005 to 0.01 gm. per kilogram of body weight caused temporary increase in the oxygen capacity and the oxygen content of the arterial blood, accompanied by a decrease in the carbon dioxide content; doses of 0.05 to 0.1 gm. per kilogram of body weight produced temporary changes the reverse of those cited above. II. Influence of Aorta Endothelial Cell Constituents on Blood Pressure. An extract of aorta endothelial cells in normal saline was injected into rabbits intravenously in doses of 0.001 to 0.1 gm. per kilogram of body weight. No marked change was observed in the blood pressure after small injections, but the largest injection of the extract caused the blood pressure to be lowered 10 to 20 mm. Hg. In experimenting with other tissue extracts the author found that after the injection of lung cell extract there was a marked lowering of the blood pressure. III. Influence of Aorta Muscle Cell Constituents on Blood Pressure. The tunica media of fresh cattle aorta was extracted with 20 per cent saline for 2 hours. This extract was injected into rabbits intravenously in doses of 0.005, 0.01, 0.05, 0.1 gm. per kilogram of body weight. Small quantities caused a slight lowering of the blood pressure which continued to fall gradually with increased doses of the extract. The blood pressure was lowered 24 to 40 mm. Hg by the injection of 0.1 gm. per kilogram of body weight. The lowered blood pressure returned to normal after 2 to 6 minutes. The depressant action on the blood pressure of the aorta muscle cell extract used in these experiments was not inhibited by atropin nor effected by cutting the vagus.

Bacteria in Anthracite Coal.—FARRELL and TURNER (*J. Bact.*, 1932, 23, 155) have examined anthracite coal taken from various levels of a mine at Pottsville, Pa., as to its bacterial content. They also examined the bacterial flora of the surface waters and soil and of the water and soil of the levels from which they procured their specimens of

anthracite. They conclude that in coal which does not contain fissures and cracks no organisms are to be found; that the positive results of early experiments are due to the filtration of organisms from the surface and mine waters by fissured and porous anthracite. This is further confirmed by the observation that the organisms found in such specimens were similar to those isolated from the water and soil surrounding, consisting chiefly of a staphylococcus and a Gram-positive spore-forming bacillus.

Intranuclear and Cytoplasmic Inclusions ("Protozoan-like Bodies") in the Salivary Glands and Other Organs of Infants.—To the growing list of newly discovered inclusion bodies, FARBER and WOLBACH (*Am. J. Path.*, 1932, 8, 123) add another example which they discovered in autopsy tissue of infants. Out of 183 infants examined 24 cases showed nuclear inclusions in the duct epithelium of the salivary glands. These inclusions are very like those described by COLE and KUTTNER (*J. Exp. Med.*, 1926, 44, 855) in the submaxillary glands of guinea pigs and by THOMPSON (*J. Inf. Dis.*, 1932, 50, 162) in the submaxillary glands of rats. These infants also showed cytoplasmic inclusions like those described by PEARSON (*Am. J. Path.*, 1930, 6, 261) in the guinea pig. In 2 instances similar inclusions were found in the parotid gland while in 2 additional cases nuclear inclusions were found in epithelial-lined spaces of liver, lungs, kidneys, pancreas and thyroid. The latter bodies are like those described by VON GLAHN and PAPPENHEIMER (*Am. J. Path.*, 1925, 1, 445) and MAGALHAES (*Arch. Path.*, 1931, 11, 561). The authors suspect the inclusion bodies represent virus infection of the infants' tissues but they are unable to correlate the presence of the inclusions with any distinctive clinical or pathologic findings.

Yellow Fever Encephalitis of the Monkey (*Macacus Rhesus*).—Since Theiler discovered the virus of yellow fever to be neurotropic for mice, Sellards has shown that the mouse virus passed serially through brains of mice becomes modified in its action upon susceptible monkeys (*M. rhesus*), in that it will then induce a fatal encephalitis in these animals when inoculated intracerebrally, without causing the usual symptoms and hepatic changes of the original yellow fever virus. GOODPASTURE (*Am. J. Path.*, 1932, 8, 137) reports a critical study of the histopathology of yellow fever encephalitis in mice and monkeys, the observations being made upon tissues supplied him by Sellards. In the mouse there is a diffuse cerebritis throughout the midcerebrum characterized by perivascular infiltration of round cells and the presence of abundant nuclear inclusions. The lesion in the monkey's brain is described as an acute, disseminated encephalomyelitis which resembles the pathologic picture of poliomyelitis in that there is marked destruction of ganglion cells accompanied by polymorphonuclear infiltration. Nuclear inclusions were detected with difficulty in 5 of 9 cases; these inclusions were few in number and often distinctly different morphologically from the typical intranuclear inclusions of yellow fever livers and mouse brains infected with yellow fever virus. The author concludes that the virus of mouse and monkey encephalitis represents a biologically modified strain of yellow fever virus which, in the monkey, is no longer productive of characteristic inclusion bodies.

The Nature of the Elementary Bodies in Psittacosis.—BEDSON (*Brit. J. Exp. Path.*, 1932, 13, 65) investigated the relation of the psittacosis virus to the minute bodies found in virulent material in cases of psittacosis, the so-called elementary bodies. The virulent material used was the spleen from infected mice in which the bodies were demonstrated. Suspensions of such spleens were centrifuged and the virus was thrown down at a rate of 5000 revolutions per minute (demonstrated by intradermal titration in guinea pigs). By fractional centrifugation and washing the virus was freed from extraneous matter. The twice washed deposit contained the virus. The only particulate matter remaining in such a deposit were minute bodies similar in every respect to those seen in preparations of virulent material. The washed bodies were agglutinated specifically by an antipsittacosis serum, and fixed complement in its presence. Antimouse spleen serum was prepared and the bodies did not react in either way with this serum. The author concluded that the minute bodies were the virus.

The Relative Incidence of Human and Bovine Tubercle Bacilli in Tuberculous Meningitis in England.—The cerebrospinal fluid from 30 cases of tuberculous meningitis occurring in England in the years 1930–1931 was examined by GRIFFITH (*J. Path. and Bacteriol.*, 1932, 35, 97). Of the 29 cases in children up to 10 years of age 20 were infected with the human tubercle bacillus and 9 with the bovine variety (31 per cent); the adult case showed bovine bacilli. Autopsies were performed on 20 of the children and the probable channel of infection determined by special examination of the regional lymph glands. In 14 the tracheobronchial glands showed the greatest enlargement and most extensive caseation; of these, 6 revealed the lungs to be primarily affected. Four cases had extensive involvement of the mesenteric glands, 1 showed tuberculous foci in the right tonsil and a cervical gland larger than the miliary lesions, and in the remaining case both the tracheobronchial and the mesenteric groups of glands were caseating. Combining the above cases and those of a previously reported series of 33, the author uses his percentage figures to estimate that in England and Wales upward of 700 persons died of tuberculosis of the central nervous system caused by bovine tubercle bacilli in each of the years, 1928, 1929 and 1930.

The Occupational Incidence of Primary Lung Cancer.—The occupations of 898 cases of primary lung cancer collected from the literature were investigated by BROCKBANK (*Quart. J. Med.*, 1932, 25, 31). The findings suggest that the incidence is greatest among the laboring classes, although no one occupation stands out. Poison gas, tobacco smoking, road dust and motor car fumes are all possible etiologic factors. The occupations of 62 cases were investigated in some detail. Nine (14.5 per cent) seemed to have definitely dusty jobs and 18 (29 per cent) worked among gases and fumes. Four were badly gassed in the war and 9 smoked excessively. The importance of more detailed investigation of the occupations of patients suffering from this disease is stressed.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Toxoid Immunization for Diphtheria.—The epidemiology of diphtheria clearly indicates that the immunization of the preschool child is the keynote for the prevention of the disease. Students of the subject are gradually being convinced that toxoid has advantages over the toxin-antitoxin mixture for this purpose. A symposium on the problem was held at the last meeting of the American Public Health Association in Montreal by a group of experts. PARK and SCHRODER (*Am. J. Pub. Health*, 1932, 22, 7) sum up as follows: Nontoxic diphtheria toxoid or anatoxin is undoubtedly the best preparation for young children and probably for older ones because it is the most potent and stable immunizing agent. Suitable underneutralized toxin-antitoxin is however an efficient preparation and is only a little less immunizing than toxoid, and it has the advantage of causing less nonspecific reactions in older children. It is to be remembered that in most toxin-antitoxin preparations the "toxin" is really mostly toxoid, since the toxin has been kept for a year or more. This allows it to become more stable and more efficient. It is difficult to decide which method should be preferred for older children. Each has its advantages. The use of toxoid mixed with lanolin, and rubbed into the skin, has a distinct place as, for example, for children in institutions or in cases in which there are objections to the use of the "needle." Alum, 0.1 or 0.2 per cent, added to the toxoid adds to its immunizing power, as is also the case when it is added to toxin-antitoxin, only then to a much less extent. It is of the greatest importance that the toxoid should be made from highly potent toxin and that the antigenic units should be stated on the containers. If it is diluted, this should be stated on the label. Toxin-antitoxin should be properly standardized and have the desired toxicity. In large cities such as New York we find toxin-antitoxin has an advantage in older children, for the injection acts not only as an immunizing dose, and gives on the average less local reaction, but because it is also a substitute for the Schick test. The exclusion of the negatively reacting children cuts down the number of later injections. For the second and third injections in these older children, either toxin-antitoxin or toxoid may be used. A Schick retest 3 to 4 months after making the immunizing injection is always desirable but not essential, for only in this way can we be absolutely sure that the desired effect has been obtained. HARRISON (*Ibid.*, p. 17) summarizes the advantages of toxoid over toxin-antitoxin mixture as follows: It is from 20 to 30 per cent more effective, even when only 2 doses are given.

It contains no serum or other animal protein likely to sensitize to a later therapeutic serum injection. It is absolutely without local or general reaction in practically all children under 7 years of age. Reactions in older children and adults are only unpleasant, not dangerous. It contains no free toxin. It is more stable, retaining its effectiveness for a longer period, and is not affected by freezing. FITZGERALD *et al.* (*Ibid.*, p. 25) state that the results in Hamilton, with a population of 150,000, and Brantford, with a population of 18,000, may be quoted as examples of municipalities that have practically eliminated diphtheria. Other experiences such as that in Windsor might also be quoted. Data from the province of Manitoba recently presented by Jackson suggest that widespread immunization in that province is a factor which accounts for the unprecedentedly low figures of diphtheria in the past year and the first months of this year. The efficiency and practicability of toxoid, properly prepared, as an immunizing agent against diphtheria, is established. POVITZKY (*Ibid.*, p. 29) states that the National Institute of Health in Washington has issued definite minimum requirements for the production and administration of toxoid, namely, the original toxin should not contain less than 5+ liters per cubic centimeter; the maximum dose should not exceed 1 cc. of the undiluted toxoid. The toxoid must protect at least 80 per cent of guinea pigs for 10 days when injected with the initial human dose against 5 m.l.d.'s.

Intestinal Carriers of Cl. Tetani and Immunity.—COLEMAN (*Am. J. Hyg.*, 1931, 14, 515) states that, in the past at least, the incidence of postoperative tetanus in gynecologic operations has been very high. The area involved is especially liable to contaminations of intestinal origin. This together with the many instances given in the literature of postoperative tetanus after laparotomies on carrier patients, assuming that modern sterilization procedures for catgut are entirely adequate, can be lead to the conclusion that the carrier state (transient or established unknown) does not immunize against tetanus. It is furthermore highly probable, at least in the majority of these postoperative abdominal infections, that the causative organism is the one harbored in the intestines. This would tend to controvert the assumption and more particularly the experimental evidence given by Tenbroeck and Bauer that type specific immunity is conferred by intestinal carriers. It must be admitted, however, that these authors stress the fact that this immunity occurs only in guinea pigs which have been carriers during a period of several months. In the present study the author fed tetanus spores to guinea pigs over a considerable period and failed to establish them in the digestive tract after 6 months. Neither antitoxin nor agglutinins for the type fed were produced in the serum of animals. The serum of these animals showed no prophylactic value against tetanus spores when injected into other guinea pigs. The animals so fed were no more immune to the intramuscular injection of spores of the type fed than were normal controls.

The Effect of Heat, Storage and Chlorination on the Toxicity of Staphylococcus Filtrates.—JORDAN, DACK and WOOLPERT (*J. Prev. Med.*, 1931, 5, 383) have amply demonstrated the toxicity of certain

staphylococcus filtrates when swallowed by man. A few preliminary attempts to test heat resistance seemed to indicate that the toxic substance was destroyed by boiling and weakened at lower temperatures (60° to 65° C.). In these tests the number of volunteers was necessarily limited, and a low dosage was used in each instance to avoid provoking a too serious reaction. At that time also the variations in the susceptibility of human volunteers toward the toxic substance were not fully appreciated. For these reasons early experiments gave results which later were recognized as somewhat misleading. Individual susceptibility is quite marked. It sometimes happens that when 2 men are given equivalent doses of an untreated staphylococcus filtrate, 1 is severely affected, the other not at all. This is particularly likely to occur if the amount given is kept close to the threshold of a possible reaction. In early tests it happened in most instances that the volunteer given heated filtrate was affected either not at all or less violently than the control volunteer given the same filtrate unheated. More extensive experience has shown that, in view of the natural variations in susceptibility, the conclusions drawn from a limited number of feeding experiments must be modified. The authors have made a number of additional observations which have shown that in some instances staphylococcus filtrates boiled for 30 minutes have produced typical and severe symptoms of this type of food poisoning. They conclude that the toxic substance is not completely destroyed at this time and temperature. Some diminution in toxic power may, however, possibly be caused by heating, even at temperatures below 100° C. Similarly, the toxic quality does not disappear after storage at a low temperature for as long as 67 days, but is perhaps somewhat weakened. Contact for 3 minutes with a rather strong dose of chlorin did not destroy the toxic quality.

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ORIGINAL ARTICLES.

THE BLOOD VOLUME IN CHRONIC ARTHRITIS.

BY M. IRVING SPARKS, M.B.,
FELLOW IN MEDICINE,

AND

RUSSELL L. HADEN, M.D.,
HEAD OF DEPARTMENT OF MEDICINE,
CLEVELAND CLINIC, CLEVELAND, OHIO.

A DISTURBANCE of the blood supply to the affected joints is apparent in many cases of chronic arthritis. Pemberton¹ has thoroughly studied this physiologic phase of the disease and has stressed its importance. Pemberton and others² have reproduced in the dog the bone changes characteristic of hypertrophic arthritis in man by ligating the vessels which carry the blood supply to the patella. In atrophic arthritis there is much clinical evidence of a diminished blood flow to the joints; the extremities are typically cold and cyanotic, and direct signs of a disturbed circulation may be obtained by studying the surface temperature and observing the superficial capillaries by means of the microscope. Fundamental improvement in the condition of a patient suffering from atrophic arthritis can usually be gauged by the state of the circulation around the joints.

Several explanations have been suggested for the diminished blood supply in the joints. Hypertrophic arthritis is often observed in association with arteriosclerosis and hypertension. In such cases the actual vascular disease may be the cause of a decrease in the flow of blood to the joints, which interferes with the nutrition of the cartilage. A marked anemia would also be an evident factor

in the nutrition of joint tissues. Increased tone of the sympathetic innervation and consequent vasoconstriction of the arterioles supplying the joints may account for a decreased blood flow as is shown by the beneficial results of ganglionectomy in properly selected cases of atrophic arthritis. It is also conceivable that an actual variation in the total volume of blood may account, in part at least, for the diminished vascularity.

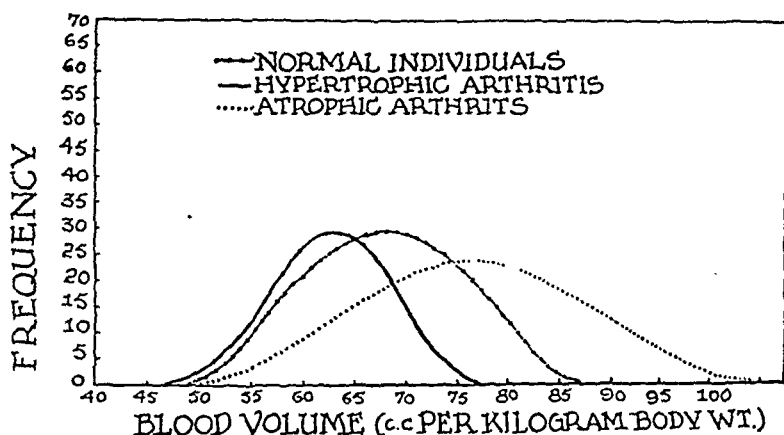


FIG. 1.—Smoothed curves of frequency distribution of blood volume determinations in normal individuals and in different types of arthritis.

To obtain further data on this last possibility, blood volume determinations have been made in 41 unselected cases of chronic arthritis of the two types.

The colorimetric method of Rowntree, Brown and Roth,³ using Congo red (National anilin, Schultz No. 307), was employed. A 1.5 per cent solution of the dye in distilled water was made each day and sterilized by bringing it to the boiling point twice. The exact amount of solution delivered from the 18-cc. graduation mark on a 20-cc. record syringe was determined and each patient was given this amount intravenously. This is an accurate and simple method for determining the exact amount of dye introduced into the blood stream. Exactly 4 minutes after the injection blood was withdrawn from the other arm without the use of a tourniquet. Rowntree employs a 2-minute interval. Other workers,^{4,5} have found that mixing is not complete under 4 minutes. The patient was kept in bed for at least $\frac{1}{2}$ hour before the test.

Normal Findings. Determinations of the blood volume were made in the case of 16 normal individuals (Table 1). The average whole blood volume was found to be 67 cc. per kg. Rowntree, Brown and Roth³ found 88.6 cc. of whole blood per kg. as the average normal for men, and 85.7 cc. for women. Another worker⁶ with the dye method reports a volume of from 84.8 to 93 cc. as normal. The results obtained by the carbon monoxid method are

much lower, however, varying from 59.47 to 71.47 per kg. Our figures for the normal by the dye method are lower than the findings of others. This might be due in part to the fact that we employ a 4-minute interval instead of a 2-minute interval. The same technique was used throughout, however, so that the comparative value of the estimations is unimpaired. We have repeated determinations on the same individuals at intervals of several months and have obtained close checks. (Table 2.)

TABLE 1.—BLOOD VOLUMES IN NORMALS.

Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
M	3936.1	67.0	2139.0	2361.7	37.5
M	4729.6	55.0	2413.6	2606.0	30.3
M	5331.5	71.1	2820.9	2345.9	31.2
M	5761.5	56.5	2216.0	2707.9	26.5
F	4107.0	72.7	2566.9	2464.2	42.5
M	4950.3	72.3	2705.1	2747.4	40.1
F	3649.6	64.0	2294.7	2080.3	36.5
M	5788.4	62.9	2643.1	3241.5	35.2
M	4227.5	68.9	...	2409.7	39.3
M	5351.7	73.8	2846.6	2782.9	38.4
F	3915.0	66.9	2509.6	2505.6	42.8
M	4517.4	57.2	2455.1	2303.9	29.2
F	3752.5	78.1	2501.3	2251.5	46.8
F	3672.4	71.3	2400.2	2247.5	43.6
F	3768.3	75.3	2479.1	2185.6	43.7
M	5047.7	64.7	2549.3	2832.8	36.3
Average	4531.6	67.0	2502.7	2504.6	37.5

TABLE 2.—SUCCESSIVE BLOOD VOLUMES IN THE SAME NORMAL INDIVIDUALS.

	Total plasma vol., cc.	Plasma, vol. per kg., cc.	Total blood, vol., cc.	Blood, vol. per kg., cc.	Blood, vol. per sq. m., cc.
Dr. R. L. S.:					
Dec. 29, 1931 . . .	2409.6	39.3	4227.5	68.9	2562.1
Mar. 13, 1931 . . .	2312.8	37.7	3920.0	63.9	2375.7
Miss R. W.:					
Feb. 6, 1931 . . .	2505.6	42.8	3915.0	66.9	2509.6
Apr. 22, 1931 . . .	2455.7	43.1	3837.0	67.3	2491.5

Findings in Arthritis. The results of determinations made in the case of 26 patients suffering from atrophic arthritis are shown in Table 3. The average blood volume is 75.9 cc. per kg. The highest volume is 112 cc. and the lowest 57 cc. per kg. This is a wide variation but in 20 cases the blood volume was between 65 and 85 cc. per kg. The average blood volume in this group of cases was found to be greater than that in the normal group; it is apparent, therefore, that a decrease in blood volume plays no part in the diminished blood flow to the affected joints.

In the group of 15 patients suffering from hypertrophic arthritis the average blood volume was found to be slightly less than that in the normal group. As shown in Table 4, the average blood volume in the hypertrophic group is 62.5 cc. per kg., with a variation of from 49.8 to 76.3 cc. There is no great variation in the average

for the series. Overweight individuals have a smaller blood volume per kilogram than normal persons. This fact probably explains our findings in this group, since patients with hypertrophic arthritis tend to be above the average weight. Only a relatively small percentage of our group of patients with atrophic arthritis were underweight, therefore a variation in weight cannot be the explanation for the increased blood volume observed in the atrophic cases.

TABLE 3.—BLOOD VOLUMES IN ATROPHIC ARTHRITIS.

Case No.	Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
2	M	4593.3	60.8	2367.7	2756.0	36.5
4	M	5582.4	66.5	2877.5	2819.1	33.6
5	M	4625.8	75.2	2705.1	2863.4	46.5
6	M	5512.6	72.5	2826.9	3015.1	39.6
7	F	3947.5	78.1	2580.1	2759.3	54.6
8	M	5042.6	72.0	2725.7	2743.2	39.2
9	F	4264.7	58.2	2352.9	2686.8	36.5
10	M	5058.4	84.3	3201.5	3490.3	58.1
14	M	4894.4	75.3	2749.6	3377.0	52.0
15	M	5065.6	73.4	2680.2	2781.0	40.3
16	F	4907.9	81.8	2956.6	3224.5	53.7
23	M	5071.8	70.2	2857.3	3093.8	46.5
26	F	3577.6	71.5	2353.7	2310.4	46.2
28	F	4670.0	57.0	2419.7	3042.2	37.1
32	M	4467.2	84.3	2713.4	2680.3	50.6
35	F	4156.4	100.1	2927.0	2909.5	70.1
38	F	3881.0	84.4	2752.4	2600.3	56.5
40	F	4667.9	68.1	2667.4	2940.8	42.9
43	M	5228.8	84.3	3022.4	3226.2	52.0
45	M	6147.8	88.4	3152.7	3713.3	53.4
46	F	3848.4	74.0	2515.3	2511.9	48.3
47	M	6252.8	112.6	3932.5	4189.4	75.5
48	F	4034.0	76.8	2689.3	2299.4	43.0
50	F	5051.3	74.3	2988.9	3384.4	49.8
51	F	3759.5	66.5	2364.5	2392.1	42.8
52	F	6050.1	57.6	2880.0	3751.1	35.7
Average		4793.1	75.9	2779.2	2983.1	47.7

TABLE 4.—BLOOD VOLUMES IN HYPERTROPHIC ARTHRITIS.

Case No.	Sex.	Blood volume, cc.	Per kg., cc.	Per sq. m., cc.	Plasma volume, cc.	Per kg., cc.
1	M	4131.8	49.8	2174.6	2148.6	25.8
3	F	3555.2	55.1	2061.7	2062.0	31.9
11	F	3500.9	66.6	2318.5	2205.6	42.0
12	M	3933.4	79.4	2675.8	2108.8	44.4
13	F	3999.7	59.2	2311.9	2439.8	36.2
18	F	4820.2	60.4	2624.5	2559.5	31.9
19	F	3527.8	52.6	2120.9	2116.7	31.6
27	F	2928.9	57.4	1952.6	1815.9	35.6
30	F	3170.8	59.1	2086.1	1870.8	35.0
31	M	3506.2	68.0	2177.8	1858.3	34.1
33	M	5344.0	63.6	2726.5	3206.4	38.2
44	F	4123.4	76.3	2767.3	2515.3	46.5
49	F	4302.2	58.9	2376.9	2710.4	37.1
37	F	3910.1	61.5	2313.7	2424.3	38.2
41	M	4646.9	65.9	2640.3	2277.0	32.3
Average		3960.7	62.5	2355.3	2293.9	36.1

The increased blood volume in the cases of atrophic arthritis is due entirely to an increase in the plasma portion. The average plasma volume is 47.7 cc. per kg., as contrasted with 37.5 cc. in normal individuals. In hypertrophic arthritis the plasma volume is 36.1 cc. per kg. The comparative figures on the total plasma and cell volumes are summarized in Table 5. In atrophic arthritis an oligocythemich hypervolemia is present and in hypertrophic arthritis there is an oligocythemich hypovolemia.

TABLE 5.—SUMMARY.

	Total blood volume, cc.	Total plasma volume, cc.	Total cell volume, cc.
Normals	4531.6	2504.6	2027.0
Atrophic arthritis	4783.1	2983.1	1800.0
Hypertrophic arthritis	3960.7	2293.9	1666.8

Since the total blood volume in atrophic arthritis is greater than that in normal individuals, with a decrease in blood in the peripheral vessels, the excess blood must be held in the large splanchnic vessels. This factor may account for the beneficial effects of breathing and postural exercises which aid in the mobilization of these large, relatively stagnant, visceral pools.

Summary. Blood volume determinations made by the Congo red method in 26 patients suffering from atrophic arthritis and 15 with hypertrophic arthritis are reported. The average blood volume in the atrophic group was found to be 11.8 per cent above the average for normal individuals, and in the hypertrophic cases 6.7 per cent below the normal average.

The increase in blood volume in atrophic arthritis is due to an increase in plasma volume, and cannot be explained on the basis of decreased body weight.

The decreased vascularity of the affected joints in atrophic arthritis cannot be due to a decrease in total blood volume.

The evident diminished blood supply to the peripheral vessels with an increased blood volume in atrophic arthritis is probably best explained by the stagnation of blood in the splanchnic pool.

REFERENCES.

1. Pemberton, R.: *Arthritis and Rheumatoid Conditions, Their Nature and Treatment*, Philadelphia, Lea & Febiger, 1929.
2. Pemberton, R.: Developments in Problem of Arthritis, *Acta Rheumatol.*, 1930, 2, 11.
3. Rowntree, L. G., Brown, S. E., and Roth, G. M.: *The volume of the Blood and Plasma*, Philadelphia, W. B. Saunders Company, 1929.
4. Smith, H. P.: The Fate of an Intravenously Injected Dye (Brilliant Vital Red), With Special Reference to Its Use in Blood Volume Determinations, *Bull. Johns Hopkins Hosp.*, 1925, 26, 325.
5. Salvesen, H. A.: Determination of Blood Volume by the Carbon Monoxide Method, *J. Biol. Chem.*, 1919, 40, 109.
6. Thompson, W. O.: Studies in Blood Volume: I. Blood Volume in Myxedema, With a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, *J. Clin. Invest.*, 1926, 2, 477.
7. Waterfield, R. L.: Changes in Blood Volume in Patients With Edema of Renal Origin, *J. Clin. Invest.*, 1931, 9, 589.

STREPTOCOCCIC AGGLUTINATION IN CHRONIC ARTHRITIS AND ACUTE RHEUMATIC FEVER.

By B. J. CLAWSON, M.D.,
PROFESSOR OF PATHOLOGY,

MACNIDER WETHERBY, M.D.,
INSTRUCTOR IN MEDICINE,

E. H. HILBERT, M.D.,

AND

H. E. HILLEBOE, M.D.,
UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MINN.

(From the Departments of Pathology, Medicine and Pediatrics.)

THE value of streptococcic agglutination in differentiating the various classes of nonspecific chronic arthritis from one another and from arthritis in any way associated with rheumatic fever has recently received important consideration as the result of the work of Dawson, Olmstead and Boots,¹ and Nicholls and Stainsby.² The results of the latter suggested different etiologic agents for proliferative arthritis, degenerative arthritis, polyarthritis following rheumatic fever, and arthritis immediately associated with acute rheumatic fever. Streptococcic agglutinins have been found in the serums in a few cases of acute rheumatic fever³ but, on account of the small number studied, no definite conclusions were reached concerning the significance of the presence of these agglutinins.

The agglutination reaction as a means of classifying streptococci has been studied by different workers in the past. The literature on this subject, which will not be discussed in this paper, has recently been reviewed in the *Annals of the Pickett-Thomson Laboratory*.⁴ It can be said, however, that the agglutination reaction has not proved a sufficient means of grouping streptococci with any degree of uniformity into classes which bear a definite relation to habitat, pathogenesis, or etiology of lesions.

Streptococci have been recovered from the blood, joints, lymph nodes, and subcutaneous nodules in a relatively high percentage of the cases of chronic arthritis, and from the blood, joints, and subcutaneous nodules in acute rheumatic fever. The frequent finding of streptococci in the above sources suggested an etiologic relationship. We attempted, therefore, to see if we could collect further evidence by the agglutination reaction from our material toward establishing the etiology of chronic arthritis and acute rheumatic fever and toward differentiating the two conditions.

Material and Methods. During the past year the many patients with chronic arthritis coming to our outpatient department for intravenous

streptococcic vaccine treatment have had their serums tested routinely for streptococcic agglutinins before treatment was begun. The streptococcic agglutination titer was determined in 300. The serums of 66 patients with acute rheumatic fever—mostly children under 10 years of age—were also tested for streptococcic agglutinins. Children were chosen in order that there might not be any confusion in diagnosis between acute rheumatic fever and chronic arthritis. It was found in controls that the age had little significance in the height of agglutination titers.

As a comparison, the serums of 110 normal individuals, 46 cases of scarlet fever, and 20 patients with glomerulonephritis were also tested for streptococcic agglutinins. The normal persons were used for controls, and the cases of scarlet fever and glomerulonephritis were included because they are quite generally considered to be due to a streptococcic infection.

We attempted to see if the findings in our material supported the belief that, in most cases, chronic arthritis and acute rheumatic fever are of streptococcic origin and that they are produced by specific strains.

In making the agglutination tests two strains of streptococci were used. Strain 1, isolated from a patient having acute rheumatic fever, had been kept on media for 9 years. It produced a slight amount of green discoloration on sheep blood agar. It cross agglutinated in high dilutions (1 to 50,000) with most other strains of acute rheumatic and chronic arthritic origins with which it was tested. The second strain, from a case of chronic arthritis, hemolyzed blood slightly at times, but was generally a methemoglobin producer. It cross agglutinated (1 to 50,000) with the rheumatic organism and with most of the methemoglobin producing strains of chronic arthritic origin with which it was tested.

Strain 2 was not used in as many tests as Strain 1 but in a sufficient number to give a fair comparison of the two strains. Both were especially suited for use, since at 37° C. they grew in a fine homogeneous suspension in beef infusion broth (pH 7.6) and did not agglutinate spontaneously. They could be kept in a weak suspension in salt solution for 24 hours or more without settling out.

The suspensions for the agglutination tests were made from the sediments of a 24- to 48-hour broth culture in 0.9 per cent salt solution. This suspension was diluted so that, when mixed with an equal amount of the respective dilutions of the serums, a faint milkyiness could be observed.

The blood for the tests was taken from a vein in the arm of the patient and stored in the ice box until the next day. The clear serum could then easily be pipetted off. The serums were diluted with salt solution as follows: 1 to 25, 1 to 50, 1 to 100, 1 to 200, 1 to 400, 1 to 800, 1 to 1600, 1 to 3200, etc. One cc. of each dilution was put into respective Wassermann tubes, and to each of the tubes was added 1 cc. of the suspension of streptococci, giving a total volume of 2 cc. in each tube. The final dilutions were twice those of the serums. The tubes were incubated in a water bath at 40° C. for 2 hours and then placed in the ice box until the next morning, when the agglutination titers were read.

The results of the agglutination tests from the groups described above are given in the following tables and descriptions. The significant differences of the statistics in the tables were checked by Pearson's Chi square formula and found to be significant.

Streptococcic Agglutination Titers in Normal Persons. The streptococcic agglutination titers were determined in 110 normal individuals with Strain 1 and in 81 with Strain 2 (Table 1). With Strain 1 the greatest number had a maximum agglutination titer

of 1 to 200. Thirty-two per cent agglutinated in dilutions above 1 to 200, but none of the 110 cases had titers above 1 to 800.

TABLE 1.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. NORMAL PERSONS.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 110 cases	5.5%	15.5%	20%	27%	21%	11%	0	0	0	0	0	Above 1 to 200, 32%.
Chronic arthritic strain, 81 cases	2%	5%	2%	18.5%	44%	26%	2%	0	0	0	0	Above 1 to 400, 28%.

With Strain 2 the greatest number showed the highest agglutination at the dilution of 1 to 400; 28 per cent had titers above 1 to 400. The highest titer was 1 to 1600, at which level 2 per cent agglutinated. Strain 2 showed streptococcic agglutination in normal persons in slightly higher dilutions than Strain 1. Strain 2 appeared to be more sensitive to agglutination than Strain 1.

Streptococcic Agglutination Titers in Patients with Chronic Arthritis. The serums of 300 patients with chronic arthritis were tested for streptococcic agglutinins with Strain 1, and 60 cases with Strain 2 (Table 2). With Strain 1 the greatest number agglutinated at the dilution of 1 to 200, the same as with normal persons; 33 per cent agglutinated above 1 to 200. The titers in chronic arthritis with Strain 1 were not higher than in normal individuals.

TABLE 2.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. CHRONIC ARTHRITIS.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 300 cases	10%	11%	22%	24%	21%	9%	2%	1%	0	0	0	Above 1 to 200, 33%.
Chronic arthritic strain, 60 cases	0	0	1.5%	7%	32%	38%	10%	10%	1.5%	0	0	Above 1 to 400, 59.5%.

The highest percentage of the 60 cases showed agglutinins with Strain 2 in the dilution of 1 to 800; 60 per cent agglutinated above 1 to 400, which was the peak of agglutination of normal persons with Strain 2. The group of chronic arthritic patients had higher titers with Strain 2 than was found in normal persons with this strain.

Streptococcic Agglutination Titers in Patients with Acute Rheumatic Fever. The agglutination titers were determined in 66 cases of acute rheumatic fever with both of the strains of streptococci (Table 3). The greatest number with Strain 1 agglutinated at 1 to 800; 48 per cent agglutinated in dilutions above 1 to 200, the peak of normal agglutination with Strain 1. The titers of rheumatic patients with Strain 1 were higher than was found with this strain in normal individuals.

TABLE 3.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. ACUTE RHEUMATIC FEVER.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 66 cases	12.5	9%	9%	21%	13.5%	23%	8%	3%	1%	0	0	Above 1 to 200, 48.5%.
Chronic arthritic strain, 66 cases	0	0	3.5%	0	7%	17%	7%	38%	17%	10%	0	Above 1 to 400, 89%.

The greatest percentage of the cases with Strain 2 had maximum agglutination titers at 1 to 3200; 17 per cent agglutinated at 1 to 6400 and 10 per cent at 1 to 12,800; 89 per cent showed agglutination in dilutions above 1 to 400, as compared with 28 per cent in normal persons with the same strain. It is evident that serums of patients having acute rheumatic fever have streptococcic agglutinins in much higher dilutions than the serums of normal persons. It is also seen that the serums of patients with acute rheumatic fever agglutinate in higher dilutions with the strain from chronic arthritis than with that from acute rheumatic fever.

As controls the serums of 46 persons with scarlet fever (Table 4) and 20 with glomerulonephritis (Table 5) were also tested for agglutinins for the rheumatic and the chronic arthritic strains. With Strain 1 the greatest number of the serums of scarlet fever cases agglutinated at the dilution of 1 to 800. The percentage agglutinating above 1 to 200 (the normal peak) was 86. The highest point of agglutination with Strain 2 was at the dilution of 1 to 6400; 90

TABLE 4.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. SCARLET FEVER.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 46 cases	0	0	4%	9%	13%	28%	19.5%	15%	9%	2%	0	Above 1 to 200, 86.5%.
Chronic arthritic strain, 46 cases	4	0	0	4%	2%	9%	17%	19.5%	33%	9%	2%	Above 1 to 400, 89.5%.

TABLE 5.—MAXIMUM STREPTOCOCCIC AGGLUTINATION TITERS. GLOMERULONEPHRITIS.

Dilutions.	Below 1 to 50.	1 to 50.	1 to 100.	1 to 200.	1 to 400.	1 to 800.	1 to 1600.	1 to 3200.	1 to 6400.	1 to 12,800.	1 to 25,000.	
Rheumatic strain, 20 cases	0	0	0	0	0	25%	45%	5%	20%	5%	0	Above 1 to 200, 100%.
Chronic arthritic strain, 20 cases	0	0	0	0	0	0	15%	15%	40%	30%	0	Above 1 to 400, 100%.

per cent agglutinated above the dilution of 1 to 400 (the normal peak).

The most common point at which agglutination took place with Strain 1 in the 20 serums from glomerulonephritis was at the dilution of 1 to 1600. All agglutinated in dilutions above the normal peak for this strain. With Strain 2 the greatest percentage of cases showed agglutination in the dilution of 1 to 12,800. All agglutinated in dilutions above the normal for this strain.

Comment and Summary. Streptococcic agglutination titers were determined in chronic arthritic and acute rheumatic fever patients for two strains of streptococci. The first strain was isolated from a case of acute rheumatic fever and the second from a case of chronic arthritis.

Comparing the agglutination titers of the above conditions with those of normal persons and of patients with scarlet fever and glomerulonephritis, with the rheumatic strain the agglutination titers of acute rheumatic patients were higher than normal, while those of the chronic arthritic patients were not. With the chronic arthritic strain the titers were higher than normal in both chronic arthritis and acute rheumatic fever, but higher in the latter. With both strains the titers were decidedly higher than normal in both scarlet fever and glomerulonephritis. In all tests, including the normal serums, the chronic arthritic strain was agglutinated in higher dilutions than the acute rheumatic strain. The chronic arthritic strain appeared to be more sensitive to agglutination.

These findings suggest that both chronic arthritis and acute rheumatic fever are streptococcic infections. The view that chronic arthritis is due to a specific strain is not supported, since the chronic arthritic strain was agglutinated in higher dilutions with serums from acute rheumatic fever patients than with the serums of patients with chronic arthritis. The lack of strain specificity is also shown by the fact that both the rheumatic and the arthritic strains were agglutinated in higher dilutions with serums from scarlet fever and glomerulonephritis than with the serums from acute rheumatic fever or chronic arthritis.

Summary. The streptococcic agglutination tests in these series suggest that both chronic arthritis and acute rheumatic fever are due to a streptococcic infection, but that neither of these diseases is produced by a specific strain of streptococcus.

REFERENCES.

1. Dawson, M. H., Olmstead, M., and Boots, R. H.: Agglutination Reactions with Hemolytic Streptococci in Rheumatoid Arthritis, *Proc. Soc. Exp. Biol. and Med.*, 1931, 28, 421.
2. Nicholls, E. E., and Stainsby, W. J.: Streptococcal Agglutinins in Chronic Infectious Arthritis, *J. Clin. Invest.*, 1931, 10, 323.
3. Clawson, B. J.: Bacteriology of Acute Rheumatic Fever, *Minn. Med.*, 1931, 14, 1.
4. *Annals of the Pickett-Thomson Research Laboratory*, 1927, 3, 101. Baillière, Tindall and Cox, London.

MONOCYTIC LEUKEMIA WITH DATA ON THE INDIVIDUALITY AND DEVELOPMENT OF THE MONOCYTE.

BY G. E. FARRAR, JR., M.D.,

AND

J. D. CAMERON, M.D.,

ANN ARBOR, MICH.

(From the Medical Service of the University Hospital, University of Michigan.)

UNTIL recently hematologists have not recognized monocytic leukemia as a separate leukemic blood picture. (See Dameshek's³ review of 18 definite cases.) All cases have had a gradual onset of fatigue, swollen gums and fever, and a rapid course of a few weeks to a fatal termination. Postmortem examination has revealed the lymph nodes, spleen and bone marrow crowded with mononuclear cells; this has been interpreted as a proliferation of the reticulo-endothelial system. A similar case, whose blood picture and progressive changes tends to clarify the nature of this entity, is the subject of this report.

Case Report. The patient, a male physician, aged 55 years, was admitted to the University Hospital on June 23, 1931, complaining of weakness and fever.

On February 1, 1931, the patient was confined to bed for 2 weeks with fever mounting to 104° F., five chills and general malaise. The fever abated and the patient felt better, but remained weak and noticed dyspnea on exertion. About 20 weeks later (June 16, 1931) his temperature rose to 103° F. following treatment for pyorrhea alveolaris, with exacerbation of his weakness and general debility, hoarseness and nocturia.

He had had the usual childhood exanthemata, and had pyorrhea for about 20 years. Several years previously he was treated for furunculosis with bacteriophage.

Physical examination showed a pale white man appearing older than his years. The conjunctiva and pharynx were injected. There was marked recession of the gums and moderate enlargement and tenderness of the submaxillary lymph nodes. A few coarse râles were heard in both lung bases posteriorly. The heart was normal in size, sounds and rate (90 per minute). The blood pressure was 120 systolic and 68 diastolic. There was no general glandular enlargement. The liver and spleen were not palpable.

The blood examination showed: hemoglobin, 50 per cent (Sahli); red blood cells, 2,480,000 per c.mm.; white blood cells, 50,000 per c.mm.; differential: polymorphonuclear neutrophils, 8 per cent; "blasts," 4.3 per cent; lymphocytes, 6.3 per cent; monocytes, 80 per cent. Many pale macrocytes were present. The platelets were scarce and a few giant forms were present.

The patient was observed for 1 day and then returned to his home for 9 days. During this period he used Fowler's solution in increasing doses, reaching 27 drops a day. His weakness on returning to the hospital was profound. He had been nauseated and had vomited on two occasions. He had a continuous headache and his temperature had reached 102° F.

every evening. Examination now (July 3, 1931) revealed: ulceration of the gums opposite the first right upper and lower bicuspid teeth following treatment of his pyorrhea with caustics; pulse, 110; respiration, 28 per minute; temperature, 103° F.; soft apical systolic murmur. Blood count: hemoglobin, 38 per cent (Sahli); red blood cells, 1,300,000 per c.mm.; white blood cells, 20,500 per c.mm.; differential: polymorphonuclear neutrophils, 11 per cent; "blasts," 3 per cent; lymphocytes, 17 per cent; monocytes, 69 per cent. The red blood cells were well colored and normal in size. The platelets were plentiful. Other laboratory findings at this time were: Kahn test negative. Agglutination for *Brucella melitensis* positive in dilution of 1 to 60; for *Brucella abortus*, *Bacillus typhosus* and paratyphosus A and B negative. Blood culture negative. Blood Group IV (Moss). The urine contained a trace of albumin, no sugar, no bile or increase in urobilinogen, occasional white blood cells, no red blood cells or casts. Stool: no occult blood. No Vincent's organisms were found in smears made from the ulcerations in the gums.

Course. The patient was kept in bed, and sedatives and mild antiseptic mouthwashes were given. He received five blood transfusions of 500 cc. each on July 5, 7, 11, 17 and 30. Following each transfusion there was subjective and objective improvement, although the ulcer in the mouth grew in size to occupy the right half of the palate and showed no signs of granulation tissue until July 13, 14 days after its appearance. By July 15 the patient was sufficiently improved to get up a short period each day. About this time, 24 weeks after onset, the spleen became palpable (2 fingerbreadths), but there was no tenderness. The liver edge was barely palpable. The blood picture showed a progressive change to July 22, 25 weeks after onset, when the count was: hemoglobin, 65 per cent (Sahli); red blood cells, 3,200,000 per c.mm.; white blood cells, 14,050 per c.mm.; differential: polymorphonuclear neutrophils, 45 per cent; "blasts," 8 per cent; lymphocytes, 33 per cent; monocytes, 14 per cent. Seven days later (July 29) a new turn in the blood picture appeared. The white blood cells increased to 24,200 per c.mm. The differential count showed: polymorphonuclear neutrophils, 26 per cent; "blasts," 47 per cent; lymphocytes, 21 per cent; monocytes, 6 per cent. At this time the patient complained that he again felt as he had at the onset of his illness, 27 weeks previously. Because many teeth were almost falling out and were exquisitely tender, those in the right upper jaw surrounding the area of necrosis were extracted on August 1, 1931, without any unusual hemorrhage resulting. In view of the reduction in the white blood cell count which occurred following the use of Fowler's solution at the time of his first admission, this was again tried.

The white blood cell count rapidly rose in a week's time from 24,200 to 155,000 per c.mm., with exacerbation of symptoms which had begun to recur the previous week associated with the increase in the number of leukoblasts in his blood. He was again confined to bed, his temperature went as high as 103° F. in the evenings and he had mild chills and drenching sweats each night. He complained of headache and oozing from his gums. He had no appetite and was nauseated and vomited on several occasions. He attributed this to the arsenic medication, although he had taken a total of only 60 drops of Fowler's solution. He now had a "catch" in his left side. Physical examination, 27 weeks after onset, showed: dyspnea, pallor, skin hot and dry, necrosis of the palate as before, gums swollen, red and oozing blood, spleen palpable (3 fingerbreadths) and tender, and slight abdominal distention.

The temperature rose as high as 104° F. with frequent chills. Blood transfusions were given on August 10 and 13 and Roentgen ray radiation was applied to the mouth, spleen and long bones on the latter date. On

August 13 purpuric spots appeared over the shoulders, bleeding from the gums became continuous and the white blood cell count increased to 210,000 per c.mm. Gross hematuria occurred on August 14 and the patient expired the same evening following 1 hour in coma with Kussmaul respiration, 28 weeks after the onset of his illness. Permission for postmortem examination was not granted.

The clinical condition during the patient's stay in the University Hospital can easily be divided into four stages: (1) That on admission, 21 weeks after onset; (2) a remission following transfusions, 24 weeks after onset; (3) an exacerbation starting 25 weeks after onset; (4) a terminal stage, 27 weeks after onset. At the beginning of this patient's illness the clinical picture was essentially the same as in the first stage, described above, 21 weeks after the appearance of symptoms.

TABLE 1.—THE BLOOD PICTURE.

Date, 1931.	Hemoglobin, per cent.	R.b.c., millions.	W.b.c., thousands.	Pmn., per cent.	Eos., per cent.	Bas., per cent.	"Blast," per cent.	Sm. Ly., per cent.	L. Ly., per cent.	M., per cent.	H., per cent.
June 23 . . .	50	2.3	50.0	8	0.7	0.3	0	3	3	80	4.3
July 3 . . .	38	1.3	20.5	11	0	0	3	17	0	69	3
4	16.0								
5 . . .	Transfusion										
6 . . .	40	1.7	20.2	10	0	0	0	11	0	80	0
7 . . .	Transfusion										
9 . . .	50	2.2	15.1								
10 . . .	55	2.4	11.4	40	1	1	5	22	3	28	2
11 . . .	Transfusion										
14 . . .	75	3.4	14.0	38	1	1	8	21	9	22	0
16 . . .	65	2.6	15.9	41	0.5	0.5	1	28	0	29	0
17 . . .	Transfusion										
19 . . .	65	3.0	17.5	37	0	0	5	25	5	30	0
22 . . .	65	3.2	14.0	45	0	0	8	18	15	14	0
25 . . .	75	2.9	16.7	41	0	0	20	32	0	7	0
29 . . .	70	3.3	24.2	26	0	0	47	20	1	4	2
31 . . .	Transfusion										
Aug. 3 . . .	65	3.0	58.2	20	0	0	46	16	6	10	2
4	61.0								
6 . . .	65	2.6	60.0								
9 . . .	58	2.9	135.0	3	0	0	86	2	0	0	9
11	155.0								
12 . . .	Transfusion										
13	210.0	1	0	0	86	3	2	3	5
14 . . .	Transfusion and Roentgen ray Death										

The Blood. During the patient's residence in the hospital the identification of the white blood cells in making the differential count on Wright-stained smears was aided by the Goodpasture¹ peroxidase technique and the vital staining methods of Sabin.²

The type cell of the blood film on first admission to the hospital—the mature monocyte—was a large oval cell, about 20 by 30 microns in size, which often showed little outpouchings of clear cytoplasm. The cytoplasm had a pale, gray-blue, foamy appearance and was dusted with azure granules which varied greatly in size. Many of these cells contained large vacuoles. The nucleus was round, horseshoe-shaped or convoluted, and stained a dark

violet. The chromatin network was very fine and there were no nucleoli. (Fig. 1, C.) Some of the monocytes were of the so-called transitional type, but the majority contained large round or oval nuclei. The peroxidase stain gave either a negative or faintly positive reaction in these cells. These cells in vital stained preparations showed neutral red granules collected in the "hof" of the nucleus and the cells had the characteristic sluggish lateral motility of the monocyte. A few histiocytes were present in the early smears and occasional leukoblasts were seen.

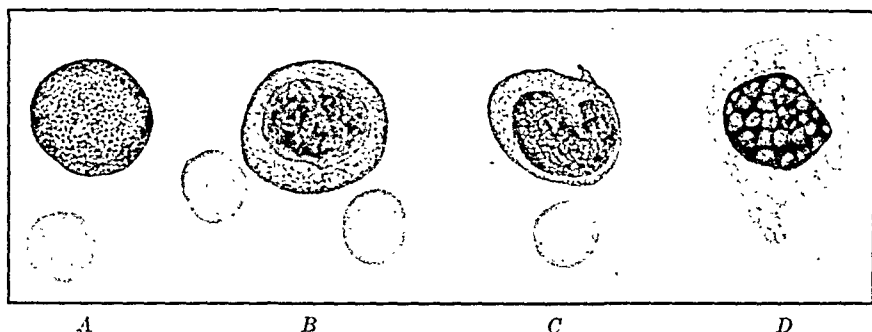


FIG. 1.—Cells from the peripheral blood. (A) Monocyte blast; (B) young monocyte; (C) mature monocyte; (D) hemohistioblast of the monocyte series. The red blood cells give comparison for the size of the cells. (Wright stain.)

As the chart shows, the number of mature monocytes gradually decreased, approaching normal absolute number, as the patient enjoyed a remission. Toward the end of this remission a younger type of cell began to appear in increasing numbers. These cells are charted as "blasts." These earlier forms were cells about 20 microns in diameter. With vital stains they were nonmotile and assumed a round or slightly oval shape containing a large round or kidney-shaped nucleus which nearly filled the cell. Nucleoli, which moved about the nucleus, could often be seen. In some of these cells large dancing cytoplasmic granules lying in the concavity of the kidney-shaped nucleus collected the neutral red stain. Most of them, however, did not contain neutral red granules. These cells did not take the peroxidase stain. In the Wright-stained preparations the cell was about 20 microns in diameter and nearly round. The large nucleus that nearly filled the cell was round, oval or indented. The fine chromatin network stained a light reddish purple and there were 2 to 4 indistinct blue-staining nucleoli. The scanty cytoplasm stained a deep, coarse ultramarine blue and there were no granules. (Fig. 1, B.)

Histiocytes were seen in nearly every smear. Several were observed under vital staining conditions. These were enormous cells in the neighborhood of 40 microns in diameter which were very actively motile, moving across an oil-immersion field in a couple of minutes. They had clear cytoplasm containing a few large Janus green granules and a small solid homogeneous-appearing nucleus which was about 10 microns in diameter. Dameshek⁴ has very well described this cell in the Wright-stained smear as a very large and irregularly shaped cell with a sky-blue cytoplasm containing vacuoles and coarse azure granules. The nucleus takes a red-purple stain and has a spongy appearance. There are several distinct blue-staining nucleoli. The peroxidase reaction is negative. (Fig. 1, D.)

The terminal stage began 27 weeks after onset with a very primitive cell in the blood films. These primitive cells made up 86 per cent of the 210,000 white blood cells per c.mm. on August 13. These cells were round or oval,

varying from 15 to 40 microns in size, with large, round, oval or indented nuclei that nearly filled the cell. The cytoplasm was very dark blue and coarse without granules. The nucleus had a very indistinct nuclear margin; the fine granular chromatin stained a faint lavender and there were several indistinct blue-staining nucleoli. (Fig. 1, A.) These cells were nonmotile. None of these cells absorbed the neutral red dye. The appearance in supravital stained preparations of these primitive cells and of the young monocytes present in the preceding phase of the disease is identical with that described by Forkner⁷ for the monoblasts and the premonocytes which he observed in the lymph nodes of intravitaly stained rabbits. The peroxidase reaction of these primitive cells was only rarely faintly positive. Several dividing cells and cells containing mitotic figures were seen. A few histiocytes were present.

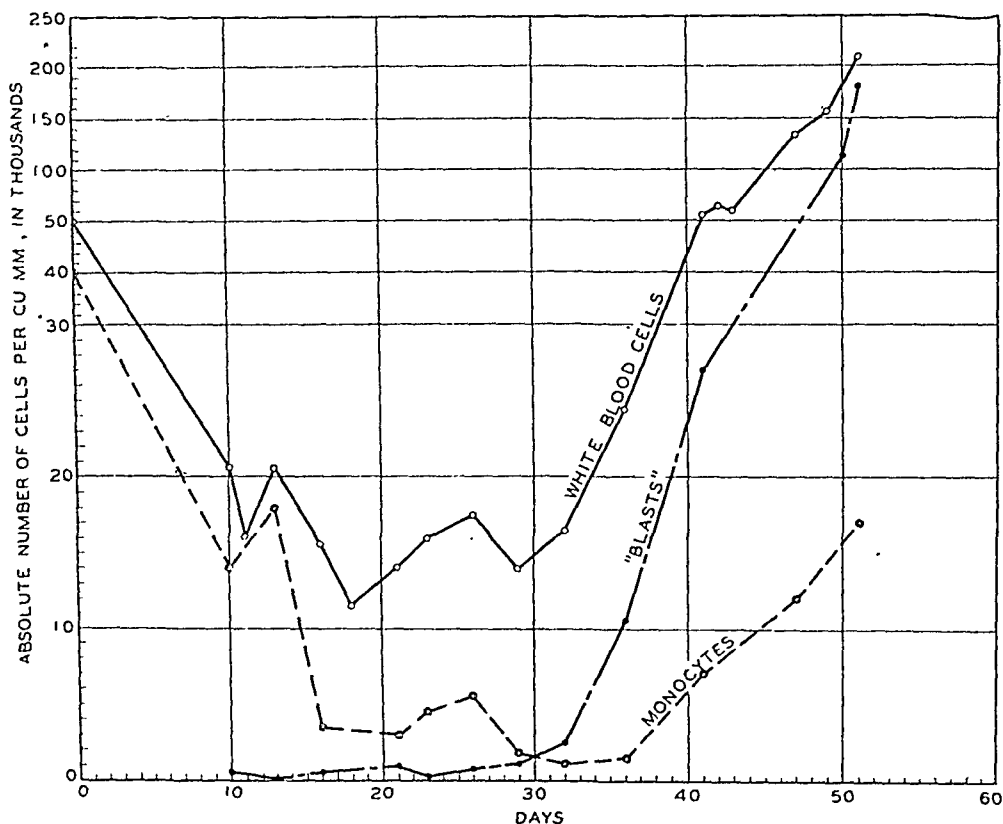


CHART I.—THE COURSE OF TOTAL LEUKOCYTES, "BLASTS" AND MONOCYTES.

Comment. What are these primitive cells? Dr. Isaacs has described these cells and the changes which took place in the character of the monocytes in this patient's blood and pointed out the differences between these primitive cells and the myeloblasts and the lymphoblasts: "These cells which resemble myeloblasts differ from them in several respects. The chromatin in the nucleus of the cells which have been stained with Wright's stain has coagulated into fine granular masses instead of the reticular type of the myeloblast or the coarsely granular type of the lymphoblast. There is no

sharply defined nuclear membrane. The cells contain multiple nucleoli. The cytoplasm stains a deep blue, and is coagulated into coarse masses. No definite granules are evident. The cell is a monocyte blast. (Fig. 1, *A*.) All gradations from this cell to the young monocyte and the adult forms can be found in the films. (Fig. 1, *A, B, C*.) The predominant cell in the early stages of the disease was the mature monocyte (transitional cell) with an indented nucleus and foamy blue cytoplasm. (Fig. 1, *C*.) As the disease progressed the more immature forms became more numerous, until at the time of death the blast stages were very common. We have here, then, a typical 'shift to the left' in the development of the monocytes, to the monocyte blast (which is a distinctive cell) and not merely a hyperplasia of the reticuloendothelial system."

As Dameshek's³ review brings out very well, many authors have felt that the monocytic blood picture and the proliferation of the reticuloendothelial system found at autopsy pointed to this system as the origin of the monocytes in the peripheral blood. The name applied to these cases in the German literature, "Reticuloendotheliose," indicates this attitude. Naegeli,⁴ however, claims that monocytic leukemia is not a separate entity; he records several cases of leukemia beginning with a monocytic picture which changes into a myeloblastic type. He further maintains that these so-called monocytes are abnormal forms of myeloblasts, for he believes that the monocytic and granular series of leukocytes have the same origin.

The cells described above which replaced the monocytes first present in this patient's blood are definitely primitive cells. If, as is held by Dameshek³ and others, the histiocyte (hematohistioblast of Ferrata, resting wandering cell of Maximow) is the precursor of the monocytic series, it is obvious to conclude, as have several authors as well as Naegeli, that such cases must have changed from a monocytic to a myeloblastic blood picture. Histiocytes were present throughout this patient's course in small numbers, but these cells are usually present in small numbers in leukemic blood pictures of all types.

In the light of the progressive change in this patient's blood cells from the mature monocyte through a stage of younger cells to a very primitive blast, and the definite differences in morphology and staining characteristics which Dr. Isaacs has pointed out between this primitive blast and the myeloblast, we feel that this case demonstrates the existence of a definite cell series separate from the granulocyte series and the reticuloendothelial system. Such a conception explains the apparent incongruity of Naegeli's⁴ cases, which changed from a monocytic to a blastic blood picture. Furthermore, consideration of the autopsy protocols describing proliferation of the reticuloendothelial system leaves considerable doubt in mind of such an interpretation. For instance, Wyshegorodzewa's⁵ description of cells of myeloblast type in the microscopic appearance of

the bone marrow, spleen and lymph nodes in a case of monocytic leukemia makes it difficult to connect these cells with reticular tissue.

"The reticulum (of the bone marrow) is poorly developed. The whole space between its meshes is filled with large cells with vesicular, round, oval or kidney-shaped nuclei with one or more nucleoli and small masses of basophilic staining nongranular cytoplasm. Among these cells are distributed cells with dark nuclei and more basophilic cytoplasm. It is impossible to connect these cells with the reticular tissue. . . . In the spleen . . . the lymphoid tissue is crowded with pale large vesicular cells which are analogous to the cells in the bone marrow. In the lymph nodes . . . are cells in large numbers of the type present in the spleen and bone marrow . . . of the type of the myeloblast."

Most reports also call attention to the absence of changes in the Kupffer cells of the liver sinusoids—one of the definite portions of the reticuloendothelial system. Naegeli's attempt to divide cases of monocytic leukemia into two types—those with and those without myeloid metaplasia of the bone marrow—is interesting in this connection. It seems to us that the findings in this case are more compatible with an acute and a chronic stage of monocytic leukemia analogous to the chronic myeloid and acute myeloblastic forms of myeloid leukemia. Wyschegorodzewa⁵ reports interesting findings in bone-marrow punctures done on the case of monocytic leukemia mentioned above during a remission and during the terminal exacerbation:

	Myeloblasts, per cent.	Monocytes, per cent.	
VIII. 23	2.6	73.2	Remission.
IX. 23	73.2	0.4	Terminal.

The predominance of "blasts" in the bone marrow as well as the peripheral blood stream characterizes the acute stage of monocytic leukemia just as in other forms of leukemia.

The excellent colored plates and descriptions of cells in the case of monocytic leukemia reported by Swirtschewskaja⁶ show a progressive change in cells from normally appearing monocyte to a cell in the terminal stage which appears like our monocyte blast. The postmortem findings in this case are very similar to those of Wyschegorodzewa,⁵ although from the published microphotographs it appears to us that undue stress is laid on the irregularity of the endothelial lining of the splenic sinuses.

Summary. 1. This is a case of monocytic leukemia which began with malaise, fever, chills, weakness and gingivitis. A period of marked improvement with residual weakness followed. The patient was first seen during his second exacerbation of symptoms when a necrotic stomatitis developed. Following several transfusions a second remission occurred. A third exacerbation of symptoms followed which rapidly progressed to a fatal terminal condition 28 weeks after the onset of the disease.

2. The blood picture changed from one with 40,000 mature monocytes (transitional forms) per c.mm. through a stage of symptomatic remission in which the white blood count reached a normal level and the differential count revealed the round nucleus type of mature monocyte in normal numbers. Before the rise in the white blood count with the third exacerbation of symptoms a less differentiated type of monocyte appeared in the blood films in increasing numbers. Immature monocytes rapidly increased in numbers and immaturity until the terminal blood film showed 180,000 primitive blasts per c.mm.—the monocyte blast—whose appearance and characteristics are different from those of the myeloblast and the lymphoblast.

3. The progressive changes in the maturity of the monocytes in this patient's blood demonstrate a third definite leukocyte series—mature monocyte, young monocyte, monocyte blast—which does not involve the reticuloendothelial system.*

NOTE.—The authors wish to express their appreciation to Dr. Raphael Isaacs for his stimulating interest and guidance in the study of this patient.

BIBLIOGRAPHY.

1. Todd, J. C.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1925, p. 323.
2. Sabin, F. R.: Bull. Johns Hopkins Hosp., 1923, 34, 277.
3. Dameshek, W.: Arch. Int. Med., 1930, 46, 718.
4. Naegeli, Otto: Blutkrankheiten und Blutdiagnostik, 5th ed., Berlin, Springer, 1931, p. 473.
5. Wyschegorodzewa, W. D.: Folia haematol., 1929, 38, 355.
6. Swirschewskaja, B.: Virchow's Arch. f. path. Anat., 1928, 267, 456.
7. Forkner, C. E.: J. Exp. Med., 1930, 52, 385.

ACUTE MONOCYTIC LEUKEMIA. A CASE WITH PARTIAL AUTOPSY.†

BY V. P. SYDENSTRICKER, M.D.,

PROFESSOR OF MEDICINE,

AND

T. B. PHINIZY, M.D.,

INSTRUCTOR IN MEDICINE,

UNIVERSITY OF GEORGIA, AUGUSTA, GA.

SINCE Reschad and Schilling-Torgau's¹ description in 1913 of acute leukemia with the monocyte as the type cell, reports of some

* The hematologic data in this case would seem to support more convincingly the belief in the existence of a third leukocytic series than that this series does not involve the reticuloendothelial system.—EDITOR'S NOTE.

† Although the cases described in this and the preceding paper are apparently of the same nature, it will be seen that a different origin for the cell concerned is suggested by the respective authors. It is felt that this juxtaposition of the two points of view should be valuable to our readers.—EDITOR'S NOTE.

28 cases have appeared under the titles "Monocytic Leukemia"^{2-12,18}, "Reticuloendotheliosis"¹³⁻¹⁶ and "Hemohistioblastic Syndrome."¹⁷ Of these only 17 have been so fully described as to appear convincing. The observations in an additional case are presented.

Case Report. Mrs. L. B. Case 71584, a white woman, aged 47 years, was admitted to the University Hospital on January 18, 1931, complaining of weakness, swelling of the left ear and an abscess over the coccyx. She gave a history of measles, scarlet fever, mumps and whooping cough during childhood. Her two pregnancies had terminated in spontaneous abortions during the third month. She had suffered from pyorrhea for 5 years. Her husband died in 1918 of pulmonary tuberculosis. She dated her present illness from November 15, 1930, when she noticed many pale bluish spots over her thighs and legs, at the time attaching no significance to them, attributing them to insect bites. On December 3 following exposure to cold she developed a severe sore throat with swelling of the glands in the left side of the neck; this lasted only 3 days. Approximately 1 week later she noticed tenderness and swelling over the coccyx followed in a few days by the development of an abscess. From December 15 she felt weak and ill and was dyspneic on exertion. There were recurrent crops of bluish spots on the skin of the body, arms and thighs. On January 3 the right upper premolar tooth was extracted on account of acute toothache and was found to be "abscessed;" following this the gums became tender and bled easily. On January 8 her left ear developed a marked painless swelling, so that hearing was impaired by closure of the external canal. On January 15 a furuncle developed in the left axilla. The discomfort occasioned by this and by her weakness caused her to enter the hospital.

Physical Examination. A strikingly pale, slightly dyspneic woman well developed and well nourished. Her temperature was 101.6° F; pulse, 100; respirations, 22. Scattered thickly over the trunk and thighs and more sparsely over the legs were innumerable purplish macules, varying from 1 mm. to 1 cm. in diameter. On both arms were remarkable annular purpuric lesions, from 2 to 3 cm. in diameter; over the extensor surfaces of the forearms these were confluent. In addition to the fresh petechiæ, there were numerous light brown stains of a previous eruption. There was no jaundice. The ankles showed slight pitting edema.

The head and sinuses were negative. The left auricle was of approximately twice normal size, thick, pale, indurated, not tender; the auditory meatus was reduced to a slit plugged with cerumen. The right ear was negative on external and otoscopic examination. The eyes presented nothing remarkable, even on ophthalmoscopic examination. The nose showed no abnormalities. The buccal mucosa was pale, the gums spongy and slightly swollen with a small superficial ulceration at the base of the lower left lateral incisor. Several teeth were missing, many were filled. The tongue was pale, coated and tremulous. The tonsils were small and pale and no pus could be expressed. The thyroid gland was normal in size and consistency. The posterior cervical lymph nodes on the left side were moderately enlarged and firm as were the inguinal glands; there was no general adenopathy.

The thorax and lungs were negative in all respects. The heart was normal and the sounds of good quality, except for soft short systolic bruits at the mitral and pulmonic areas. The heart rate was increased. The peripheral arteries felt soft. The blood pressure was 120 systolic and 100 diastolic.

The abdomen was flat; there was no lateral bulging; there was the old

scar of a McBurney incision. The liver was slightly enlarged (from fifth rib to 4 cm. below the costal margin). The spleen could not be felt, although the area of splenic dullness was thought to be moderately increased. The kidneys were apparently normal. There was no evidence of free peritoneal fluid.

The external genitalia showed marked edema of the labia minora and a small amount of thick, yellow vaginal discharge. Over the tip of the coccyx was a resolving furuncle. Rectal examination was negative.

The extremities were negative, except for the eruption and edema described. In the left axilla was a small furuncle and the adjacent axillary lymph nodes were moderately enlarged. The reflexes were normal.

Laboratory Examinations. The blood showed 55 per cent hemoglobin (Sahli); 2,960,000 erythrocytes; color index, 0.9; 150,000 platelets and 71,500 leukocytes per c.mm.; neutrophils, 2.7 per cent; eosinophils, 0.1 per cent; basophils, nil; myelocytes, 0.2 per cent; myeloblasts, 0.2 per cent; lymphocytes, 11.4 per cent; monocytes, 81.8 per cent; "immature" cells, 3.2 per cent; smudges, 1.4 per cent (500 cells, Jenner-Giemsa stain). The predominating cells were monocytes of the type ordinarily seen in normal blood: Large cells, from 12 to 20 microns in diameter, with abundant gray-blue spongy cytoplasm, irregular fine azure granulation and occasional vacuoles. The nuclei stained purple, with the exceptions noted below, and were rather coarsely reticulated with definite marginal condensation of the chromatin and no nucleoli. Some 35 per cent of these cells contained round or oval nuclei; of these the majority exhibited typical morphology and color. A small percentage had nuclei which were slightly larger and which stained violet rather than purple; the chromatin network was finer and there were occasional nucleoli. The remaining 65 per cent of monocytes had lobed or convoluted nuclei of varying complexity but with typical reticulation and no nucleoli. Very many of the cells of both groups were irregular in shape, elongated, "tailed" or with marked peripheral budding. The 3.2 per cent of cells classified as "immature" were believed to be young monocytes. These were large cells, 15 to 40 microns in diameter, quite irregular in outline, some round, some oval, many bizarre in shape with buds, pseudopodia and elongated streamers of cytoplasm. The cytoplasm was abundant, definitely reticulated or spongy, gray-blue, taking a more basophilic stain than the mature monocytes. Azure granulation was infrequent and, when present, the granules were massed near the nucleus, usually in clumps on opposite sides of the cell leaving the periphery ungranulated. A small number of the round and oval cells contained Auer bodies, and in some instances these seemed to be breaking up into azure granules. The nuclei were large, violet staining, round or oval and frequently eccentrically placed. The reticulum was extremely fine, giving a homogeneous appearance quite different from the even stippling of the myeloblastic nucleus; there was definite peripheral condensation of the chromatin and 1 to 3 nuclei were quite regularly present. In many of the larger cells the nuclei showed several or many buds; this phenomenon seemed not to be associated with mitosis.

The neutrophils showed no noteworthy abnormalities. The occasional myeloblasts and myelocytes were quite typical in form and tinctorial reactions. The lymphocytes were largely of the small type. Very rarely a large oval deeply basophilic plasma cell was seen.

Peroxidase stains (Goodpasture) showed that 67 per cent of the monocytic cells were oxidase negative and 33 per cent positive; the reacting granules were scanty and exceedingly small.

With supravital staining by Sabin's method the cells classified as monocytes reacted typically; neutral red appeared in fine granules clustered near the nuclear incisures of cells with lobulated nuclei and scattered through

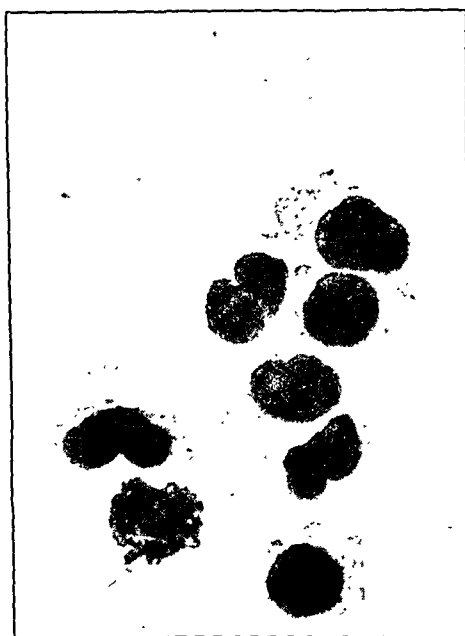


FIG. 1.—Group of mature monocytic cells showing strikingly irregular outlines.
($\times 900$.)

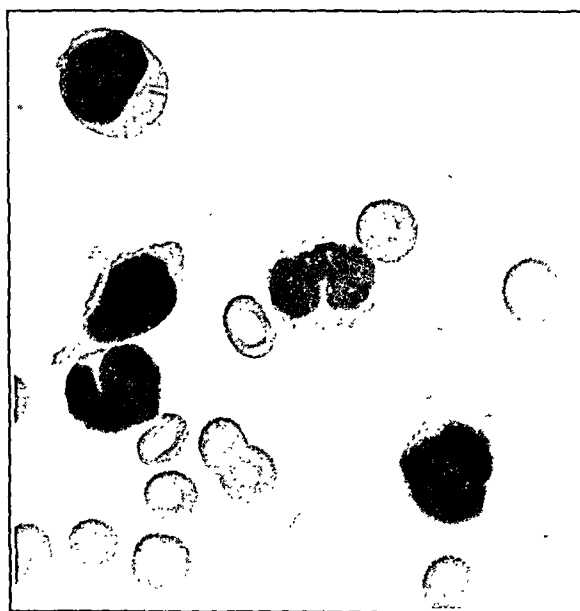


FIG. 2.—Tailed or racquet forms. Immature monocyte with Auer bodies at upper left of field. ($\times 1250$.)



FIG. 3.—Immature monocyte with nuclear excrescences. ($\times 1250$.)

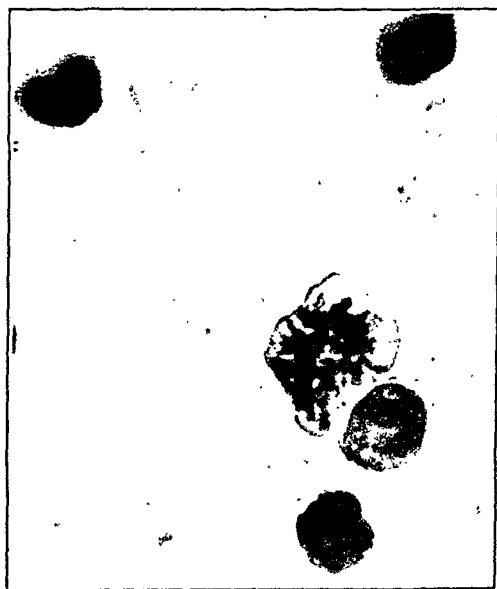


FIG. 4.—Mitotic form. ($\times 1250$.)



FIG. 5.—Smear from bone marrow. ($\times 1250$.)



FIG. 6.—Smear from spleen. ($\times 1250$.)

the cytoplasm of cells with round nuclei. Both types of cells were actively motile on the warm stage. The larger "immature" cells showed coarser granulation without tendency to clumping, motility was marked and it seemed that all gradations between them and typical monocytes could be seen. The picture of cellular motility presented by these preparations was in striking contrast to that of immobility seen in myeloblastic leukemia.

The erythrocytes presented little of note; there was slight anisocytosis and poikilocytosis with moderate central pallor. Many cells showed diffuse basophilia and there were a very few normoblasts; reticulocytes numbered 6 per cent (brilliant cresyl blue). The platelets were diminished in number and were mostly larger than normal. The bleeding time was 3 minutes (Duke's method); the coagulation time, 5 minutes (Lee's method). The red cells were normally resistant to hypotonic sodium chlorid solutions, hemolysis beginning at 0.42 per cent—complete at 0.2 per cent.

The blood glucose was 100 mg. per 100 cc.; the nonprotein nitrogen, 23 mg. There was no increase in bile pigment in the blood. The Wassermann reaction was weakly positive (2+) and the Kahn and Hinton tests strongly positive on 2 occasions. The urine was constantly of low specific gravity, contained traces of albumin and a few casts from time to time, usually in association with febrile exacerbations; 45 per cent of phenol-sulphonaphthalein was excreted during the test period. The sputum was negative for tubercle bacilli. The stools showed nothing of importance.

This patient remained in the hospital until her death on March 13, 1931. There was continuous elevation of temperature from 99° to 104° F., with an irregular diurnal variation. There were repeated eruptions of purpuric spots and, during the last 3 weeks of life, marked infiltration of the skin of the trunk and thighs. The spleen was never felt; the liver and lymph glands did not change in size. Blood cultures in various media taken on January 23 and 25 and February 15 remained sterile. A roentgenogram of the thorax made on February 5 showed no evidence of mediastinal or pulmonary infiltration. On account of progressive anemia transfusions of blood were given on February 11 and 18. Her condition failed rapidly, and after March 1 she was completely prostrated and almost constantly delirious. After March 3 there was a marked diminution in the amount of fever, her temperature never rising above 100. On March 11 a pleural friction was heard over the left back, and on the following day there were signs of a considerable accumulation of fluid. Death occurred on March 13; no autopsy was allowed, though permission was granted to remove a portion of a rib. Small specimens of skin and spleen were secured also and it was seen that the spleen was of approximately twice normal size.

The details of daily blood examination are shown in Table 1. Anemia became profound during the third week of observation, the hemoglobin falling to 15 per cent and the erythrocytes to 900,000; following transfusion there was some improvement which persisted for 2 weeks. There was never evidence of marked erythropoiesis, though the reticulocytes were constantly increased to 6 or 7 per cent. The number of leukocytes was exceedingly variable, wide fluctuations occurring from day to day. The count fell rapidly after admission, reaching 12,000 on January 28; from this date until February 25 there was at no time any marked leukocytosis, and on 1 day the count was 3500. After February 26 there was a rapid rise with variations between 20,000 and 60,000 leukocytes until the last few days of life when there was a sudden increase to over 100,000. During the entire period of observation there was a relative and absolute neutropenia and paucity also of other polymorphonuclear types. The lymphocytes showed a marked absolute increase though the relative percentage was at times low. Care was exercised to avoid confusing lymphocytes with micro-

myeloblasts and the counts were checked frequently with peroxidase and supravital stains. The total percentage of monocytic cells, combining mature and immature forms, varied from 49 to 93 per cent, remaining between 70 and 85 per cent during most of the observation period. In the last week of life the relative number of immature monocytic cells increased greatly; occasional mitotic figures were observed and in a few smears monocytes were seen which had phagocytosed erythrocytes; phagocytosis was not

TABLE 1.—DAILY BLOOD EXAMINATION. (DIFFERENTIAL COUNT, 500 CELLS, JENNER-GIEMSA STAIN.)

Date.	Hemoglobin, per cent.	Erythrocytes millions.	Leukocytes thousands.	Neutrophils.	Eosinophils.	Basophils.	Lymphocytes.	Monocytes.	Immature cells	Myelocytes.	Myeloblasts.	Plasma.	Smudges.
Jan. 20	55	2.9	71.2	2.7	0.1	0	11.4	81.8	3.2	0.2	0.2	0	1.1
22	35	2.3	55.2	0.7	0	0	13.0	80.5	3.0	0	0.3	0	3.0
23	70.0	2.2	0	0	10.8	80.9	3.7	0	0.1	0	2.3
24	21.4	5.3	0	0	16.0	73.0	5.0	0	0.1	0	0.4
25	30	...	24.3	2.0	0	0	18.0	77.5	2.0	0	0.2	0	0.3
26	23.3	8.0	0	0	21.0	68.0	2.1	0	0.1	0	0.3
27	28	...	22.5	2.4	0.3	0	12.4	79.2	3.4	0	0.1	0	2.2
28	12.8	3.8	0	0	14.0	78.0	2.8	0.1	0.2	0.1	1.0
29	17.6	2.3	0.1	0	12.0	77.9	2.6	0	0	0.1	5.1
30	12.0	3.0	0	0	15.0	77.0	3.4	0	0.1	0	1.5
31	20	1.7	14.2	9.6	0	0	40.2	46.8	2.6	0.1	0.2	0.1	0.4
Feb. 1	13.2	9.0	0	0	16.0	72.0	3.2	0.1	0.1	0	1.6
2	8.0	7.4	0.2	0	16.2	72.0	1.4	0	0	0.3	2.6
3	8.4	8.8	0.6	0	22.6	65.0	0.6	0	0.2	0.8	1.4
4	...	1.0	14.8	8.2	0	0	20.2	63.0	4.6	0	0.4	0.4	0
5	15	0.9	11.6	6.0	0	0	18.0	70.0	4.6	0.2	0.4	0	0.8
6	22	1.6	8.8	6.0	0	0	17.0	74.0	2.8	0.1	0	0	0.1
7	25	1.7	6.0	7.2	0.2	0	25.6	63.2	1.4	0	0.4	0	1.8
8	15	1.0	9.0	6.0	0	0	24.0	61.0	8.0	0.1	0.3	0.1	2.5
9	20	1.4	10.7	7.0	0	0	19.0	66.0	7.4	0	0.1	0	0.5
10	22	1.7	10.9	6.5	0	0	16.5	68.5	8.5	0.1	0.1	0	0.3
11*
12	30	2.2	7.6	5.8	0	0	21.8	67.6	1.6	0	0.2	0.2	2.8
13	35	2.5	9.2	4.4	0.6	0	21.4	67.6	2.2	0	0	0	0.8
14	8.3	10.0	0.4	0	30.6	54.6	2.2	0.2	0.4	0.6	0.8
15	30	1.7	15.4	7.0	0	0	20.0	67.0	2.0	0	0.2	0.2	1.6
16	30	1.4	9.2	8.0	0	0	16.0	71.4	3.6	0	0.1	0.1	0.8
17	30	1.6	9.8	8.2	0.2	0	35.6	53.0	2.0	0.2	0.2	0.4	0.2
18†
19	32	1.7	13.8	7.2	0	0	24.0	65.4	2.5	0.3	0	0	0.6
20	30	1.6	10.2	4.0	0	0	20.0	72.0	2.5	0.1	0.2	0.2	1.0
21‡
22	35	1.8	14.0	2.0	0	0	21.0	71.0	4.3	0	0.2	0	1.5
23	35	2.0	12.4	0.5	0	0	15.5	69.2	14.0	0.2	0.4	0	1.2
24	35	1.9	3.5	1.0	0	0	15.0	68.0	15.4	0.2	0.2	0	0.2
25	30	1.2	17.0	2.0	0	0	14.0	73.4	8.4	0	0.2	0.1	1.9
26	30	1.3	35.0	4.0	0	0	23.2	63.2	7.8	0	0.4	0	1.4
27	25	1.2	50.4	0.5	0	0	12.5	78.6	6.4	0.2	0.6	0	1.2
28	28	1.6	50.8	0.5	0	0	5.5	83.4	8.6	0.2	0.4	0.1	1.3
Mar. 1	25	1.4	50.0	0.5	0	0	4.6	89.0	3.8	0	0.2	0.1	1.8
2	30	1.8	53.0	4.8	0	0	11.2	82.0	2.0	0	0.4	0	0.6
3	30	2.0	22.0	4.2	0.6	0	16.4	74.0	3.0	0	0.2	0.2	1.4
4	28	1.6	21.2	3.2	1.0	0	14.4	64.0	11.8	0.4	1.0	0.2	2.0
5	25	1.3	64.0	5.2	1.0	0	17.2	59.6	15.0	0	0.8	0.2	1.0
6	20	1.2	56.0	7.0	0	0	14.0	58.0	16.4	1.0	0.2	0.1	3.3
7	20	1.1	41.2	6.0	0.6	0.2	16.4	66.4	9.2	0.2	0.4	0.2	1.0
8	25	1.7	60.8	6.0	0.8	0	12.8	59.8	18.6	1.0	0.2	0.4	2.2
9	20	1.5	124.0	4.2	0	0	5.0	69.2	16.8	1.6	0.4	0	2.8
10	20	1.2	132.0	2.8	0.2	0	11.2	61.0	18.0	0.4	1.0	0.2	2.2
11	25	1.6	128.0	4.8	0.4	0	9.6	65.0	17.4	0.8	0.6	0.4	1.0
12	25	1.6	160.0	2.2	0	0	6.0	64.0	21.4	1.4	1.2	0	0.8
13	168.0	2.5	0.1	0	3.9	59.4	28.9	0.5	0.3	0	4.4

* No count on this day. Transfusion, 350 cc.

† No count on this day. Transfusion, 300 cc.

‡ No count on this day.

uncommon in vitally stained preparations. The cells classified as immature monocytes corresponded in size, structure and staining reactions both in fixed and vitally stained preparations to the "hemohistiocytes" of Ferrata and the "histiocytes" described in Dameshek's cases. Included in the immature classification were very large cells with irregular, indistinct outlines, pale gray-blue cytoplasm and very large round or oval nuclei with extremely coarse reticulation. These could not be identified in vitally stained preparations and in smears they tended to occur in groups; for these reasons they were considered to be slightly damaged immature monocytes.

The myeloblasts and myelocytes which were constantly present in very small numbers were typical and bore no resemblance to the monocytic cells nor could transition forms between the two classes be seen. The plasma cells were very large, deeply basophilic, oval or irregular in contour, with large, round, eccentric, coarsely reticulated nuclei. The dark blue spongy cytoplasm not infrequently contained coarse angular azure granules.

The bone marrow was gray and dry. Smears showed immense numbers of cells identical with those predominating in the blood. Only occasionally could a myelocyte or polymorphonuclear cell be seen. Sections showed that the normal marrow structure was obliterated by masses of large mononuclear cells which seemed to have squeezed out all other types. The fragments of spleen secured were too small to give a satisfactory histologic picture. Masses of monocytes were present, but their relation to the splenic architecture could not be determined. Smears from the splenic pulp showed nothing but monocytes and erythrocytes; these smears were, in fact, almost indistinguishable from the marrow smears. Sections of the skin showed massive infiltration of the corium with large mononuclear cells; these had accumulated particularly around the sweat and sebaceous glands and in the perivascular connective tissue.

Discussion. The literature on monocytic leukemia has been reviewed recently by Dameshek,¹² who collected all cases on record up to the time of his publication. His critique of case reports appears to be accurate, except that he includes 3 cases recorded by Rosenthal⁵ whereas only 1 of these is given in sufficient detail to make the diagnosis unquestionable. The clinical manifestations of monocytic leukemia are not essentially different from those of other acute leukemias; a septic type of fever, stomatitis of some degree, purpura and marked anemia have been quite constant. Splenomegaly is not usual, though it was marked in the cases of Reschad and Schilling-Torgau,¹ Merklen and Wolf,⁸ Hannema¹⁰ and Swirtschewskaja.¹⁵ In all other instances the spleen was only slightly enlarged or was not felt. Slight to moderate enlargement of the liver has been noted in every case. Adenopathy is quite variable; when present, it has been localized in the cervical region; it does not seem to form a part of the picture. The number of leukocytes has varied widely, from 1,900¹¹ to 416,000.¹⁵ Sudden marked changes in the count seems more frequent than in other types of acute leukemia and an *hiatus leukemicus* has been noted frequently. The proportion of monocytes has varied from 44 per cent³ to 99 per cent⁸ with an average of approximately 80 per cent.

Necropsies, more or less complete, have been done in 13 cases. In all there has been widespread infiltration of the tissues with monocytic cells. The lymph glands, liver, spleen and bone marrow show the most marked disturbance. The normal histology of the lymph glands and spleen is destroyed, there is proliferation of the reticulum cells and of the endothelium of the sinuses of the spleen with some evidence of actual "desquamation" of new-formed monocytes into the blood stream. In the liver the reticuloendothelial tissue is hyperplastic and the liver capillaries are crowded with monocytic cells. The bone marrow shows what may be called "monocytoid metaplasia"¹² the normal structure being obliterated by intense monocytic infiltration. The skin shows marked infiltration of the deeper layers, particularly around the glandular structures. The perivascular connective tissue of many organs shows extreme monocytic infiltration.

The diagnosis rests on the recognition of the type cell as the monocyte, either mature or immature. The adult monocyte can usually be identified without difficulty in well-stained preparations by its morphology and staining reactions. The immature monocytes ("monoblasts" of Merklen and Wolf,⁸ "hemohistioblasts" (?) of Ferrata and Reitano,¹⁷ "histiocytes" of Dameshek¹²) offer more difficulty. The large size, abundant gray-blue cytoplasm and large finely reticulated nucleus of these cells make them striking objects in fixed smears. Supravital staining is characteristic and is the most important diagnostic procedure, differentiating them satisfactorily from cells of the myeloblastic series.

Monocytic leukemia must be differentiated from other acute leukoses, in particular from certain cases of acute myeloblastic leukemia in which there is a predominance of myeloblasts with lobed nuclei. Infectious mononucleosis may at first arouse suspicion of this condition but the absence of immature forms and the benign progress of the disease should speedily remove doubt, the same being true of the mononucleosis following administration of arspenamin. Agranulocytosis has doubtless been confused with monocytic leukemia,⁷ but in the latter condition there is never a complete absence of granular leukocytes nor do immature monocytes occur in agranulocytosis.

The acceptance of monocytic leukemia as a clinical and pathologic entity involves recognition of the validity of the newer conception of the derivation of the circulating monocytes directly from reticuloendothelial tissue. The investigations of Kiyono,¹⁹ Maximow²⁰ and Sabin^{21,22} have gone far toward the proof of this theory which has been advanced by numerous observers and which offers a logical classification of leukemic monocytosis as a systemic disease. The occurrence of myeloblasts and myelocytes, particularly in the later stages of the disease, has led many authors to classify these cases as

unusual types of myeloses. Naegeli²³ is a vigorous exponent of this view. It seems more reasonable to assume that the intense monocytic proliferation in the marrow forces a certain number of immature marrow cells into the circulation, and this assumption seems strengthened by the constant occurrence of a marked actual as well as relative granulocytopenia.

Conclusions. A case is recorded in which the diagnosis of acute monocytic leukemia was made. Although multiple infections were present, negative cultural studies and the course of the disease seemed to eliminate pyogenic infection as a cause of the blood picture.

The type cell in both mature and immature stages was adequately identified with peroxidase and supravital as well as the conventional stains. It was differentiated from cells of the myeloid and lymphatic series as belonging to the monocyte series.

A direct derivation of the monocyte from the reticuloendothelium offers a logical explanation of the occurrence of this type of leukemia.

NOTE.—Since the preparation of this paper additional instances have been reported by Cooke, W. E., *Lancet*, 1931, 2, 129; Lawrence, P. S., Posey, A. I., and Young, M. W., *Folia hematol.*, 1931, 44, 332; Rirks, W. W., Jr., and Cunningham, R. S., *South. Med. J.*, 1931, 24, 1089.

REFERENCES.

1. Reschad, H., and Schilling-Torgau, V.: *München. med. Wehnschr.*, 1913, 60, 1981.
2. Fleischmann, P.: *Folia hæmatol.*, 1915, 20, 19.
3. Bingel, A.: *Deutsch. med. Wehnschr.*, 1916, 42, 1503.
4. Komiya, E., and Hayishi, T.: *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo*, 1921, 27, 375.
5. Rosenthal, N.: *Med. Clin. North America*, 1921, 4, 1607.
6. Ewald, O., Frehse, K., and Hennig, G.: *Deutsch. Arch. f. klin. Med.*, 1922, 138, 353.
7. Hoff, F.: *Virchow's Arch. f. path. Anat.*, 1926, 261, 142.
8. Merlden, M., and Wolf, M.: *Presse méd.*, 1927, 35, 145.
9. Alder, A.: *Folia hematol.*, 1923, 29, 105.
10. Hannema, L. S.: *Nederl. tijdschr. v. geneesk.*, 1928, 1, 2281.
11. Wyschegorodzowa, W. D.: *Folia hæmatol.*, 1929, 38, 355.
12. Dameshek, W.: *Arch. Int. Med.*, 1930, 46, 718.
13. Ewald, O.: *Deutsch. Arch. f. klin. Med.*, 1923, 142, 222.
14. Ugriumov, B.: *Zentralbl. f. allg. Path. u. path. Anat.*, 1928, 42, 103.
15. Swirtschewskaja, B.: *Virchow's Arch. f. path. Anat.*, 1928, 267, 456.
16. Hittmair, A.: *Folia hæmatol.*, 1928, 37, 321.
17. Ferrata, A., and Reitano, D.: *Hæmatol.*, 1923, 4, 385.
18. Clough, P. W.: *Trans. Assn. Am. Phys.*, 1931, 46, 258.
19. Kiyono, K., and Nakano, T.: *Acta scholæ med. univ. imp. Kioto*, 1919-1920, 3, 55.
20. Maximow, A.: *Ann. d'anat. path.*, 1927, 4, 701.
21. Sabin, F.: *Bull. Johns Hopkins Hosp.*, 1923, 34, 277.
22. Sabin, F., Doan, C. A., and Cunningham, R. S.: *Carnegie Inst. Contrib. Embryol.*, 1925, 16, 125.
23. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, 5th ed., Berlin, Julius Springer, 1931.

THE HEMATOPOIETIC RESPONSE IN PERNICIOUS ANEMIA
FOLLOWING THE INTRAMUSCULAR INJECTION OF
GASTRIC JUICE.*

By ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE,

LEON SCHIFF, M.D.,

ASSISTANT PROFESSOR OF MEDICINE,

GEORGE BURGER, M.D.,

AND

JAMES E. SHERMAN, M.D.,

ASSISTANTS IN MEDICINE,

UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

(From the Department of Internal Medicine.)

THE treatment of pernicious anemia has undergone rapid advance in recent years. The introduction of the liver diet by Minot and Murphy¹ was the first great step forward, and was soon followed by liver extract.² Working on an original theory, Sharp³ introduced hogs' stomach (ventriculin), which Sturgis and Isaacs⁴ proved to be efficacious therapeutically. Quite independently, Conner⁵ and Wilkinson⁶ also employed hog's stomach in the treatment of the disease. Later, Gänsslen⁷ and Castle^{8,9} prepared liver extracts for parenteral use.

Achylia gastrica has long been considered to be an important diagnostic criterion of pernicious anemia. The illuminating studies of Castle¹⁰⁻¹⁴, however, have thrown new light on the importance of this factor. He and his coworkers have shown that there is an unknown substance present in normal gastric juice which is lacking in the secretion of the stomach in pernicious anemia. They have shown that the feeding of beef which has been digested by normal gastric juice causes a reticulocyte response in pernicious anemia, whereas beef digested with gastric juice from a patient with pernicious anemia has no such effect. Further, during a remission, the gastric juice of the patient with pernicious anemia becomes active, like normal gastric juice. It was further demonstrated that feeding of 300 cc. of normal gastric juice without beef daily for 10 days was ineffective.

The unknown substance is destroyed, they have shown, by boiling for 5 minutes, by heating to 70 to 80° C. for a half hour or by exposure to a temperature of 40° C. for 3 days.

As a result of these brilliant researches, it seemed to us quite possible that the normal stomach secretes a substance (probably

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the same substance which Castle has shown to be present) which, while without effect on the reticulocytes when administered orally, might cause a response if it could be administered parenterally. In order to test this theory, we^{15,16} proceeded as follows: Normal gastric juice was collected from patients free from anemia following lavage and the administration of histamin. The juice was rendered neutral to litmus, and after cultures had proved sterility, it was injected intramuscularly, first in rabbits and later in man, without undue local or general reaction. Autopsy revealed no lesions in the muscles of rabbits at the site of injection. A patient dying of acute leukemia into whose gluteal muscle gastric juice was injected came to autopsy. Microscopic examination of the muscle showed no noteworthy change. Intravenous injections were tried, but were abandoned temporarily because of rather severe general reactions.

Next, neutralized sterile juice was given intramuscularly in amounts up to 20 cc. to a patient with pernicious anemia. The reticulocyte response was so slight as to be negligible, though sufficient to warrant further study. Attempts were now made to concentrate the gastric juice. This was done by allowing it to evaporate in dishes placed in the incubator at 38° C. to about 3 to 5 per cent volume. This required between 2 and 3 days. We secured a preparation with definite activity, one which gave an increase of reticulocytes to about 6 per cent in a patient who had 1 million red cells. The response was quantitatively far below that obtained with liver extract or ventriculin. But the publication of Castle's observations on the effect of heat on the unknown substance, particularly its destruction by exposure to 40° C. for 3 days, made it seem probable to us that our material had been partially inactivated in our method of concentration. On the advice of Dr. G. E. Cullen of the Department of Pediatrics, whose helpful suggestions we acknowledge gratefully, vacuum distillation of the gastric juice at a temperature not exceeding 40° C. was tried. By this method it is possible to reduce the volume to about 3 per cent in 2 to 4 hours.

Normal human gastric juice, concentrated by distillation *in vacuo*, was now given to patients with pernicious anemia. The injection of the equivalent of 450 cc. of gastric juice to a patient with 2.1 million red cells led to a reticulocytosis of 17.6 per cent in 36 hours. Twelve days after the injection, the red count and percentage of hemoglobin began to increase. Within the period of the next 12 days, the count increased by 1.5 million cells and the hemoglobin by 20 per cent. The count then remained stationary until further treatment was instituted. A second patient who received intensive intramuscular treatment with Lilly's liver extract No. 343, improved after this until the red count reached 4.1 million, where it remained for 4 weeks, despite daily intramuscular injections of 4 cc. Then, an intramuscular injection of the equivalent of 300 cc. of human gastric juice was given. Within 14 days, the red count had increased

to 5.1 million and the hemoglobin had risen from 76 per cent to 88 per cent when the patient was discharged. The reticulocytes rose from 0.5 per cent to 2.7 per cent within 9 hours after the injection.

The results obtained in these patients prove the presence in normal gastric juice of a powerful bone marrow stimulant, one which produces not only a marked and very rapid reticulocyte increase after intramuscular injection but also rapid maturation of the red cells.

With the reticulocytosis, we have also found a still earlier increase in red cells containing nuclear particles. The majority of the latter are minute, about pin-point in size. The cells containing them are usually polychromatophilic and the reaction is looked upon as analogous to the reticulocytosis.

There is also an increase in the total white count and in the percentage of neutrophil cells within a few hours after the injection, as well as an increase in the number of blood platelets. This reaction subsides within 1 to 2 days. Following the injection, the eosinophils gradually increase, reaching the peak usually on the fifth day.

In the process of concentration of human gastric juice *in vacuo*, a sediment forms. Injection of this sediment is not followed by an increase of the reticulocytes. The supernatant fluid, on the other hand, is highly active.

Boiling the supernatant fluid for 5 minutes destroys the substance which causes the reticulocytosis and the increase in nuclear particles. But it is noteworthy that injection of the boiled supernatant fluid produces a prompt neutrophilic leukocytosis. Therefore, the substance causing reticulocytosis is not that which causes the neutrophilic leukocytosis.

The unknown substance present in normal gastric juice is dialysable, passing through a collodion sac. In this connection it is of interest that the anti-anemic factor of stomach tissue is also recoverable in the dialysate.¹⁷ This indicates that its molecular structure is relatively simple. That the increase in red cells and hemoglobin, once begun, does not continue until normal values are reached shows that it is exhaustible and, therefore, probably not an enzyme. It is soluble in acetone.

More recently, through the coöperation of Dr. E. A. Sharp, Director of the Department of Experimental Medicine of Parke, Davis and Company, we have obtained the gastric juice of swine. With this material, we have obtained an increase in the reticulocytes in pernicious anemia, the results being analogous to those obtained with human gastric juice, though less pronounced quantitatively. We have noted the same increase in nuclear particles, the neutrophilic leukocytosis and the increase in blood platelets, though the response has been less prompt. With certain modifications in the method of preparation, it has been possible to obtain a product from swine which produces no leukocytosis, a slight local reaction with

practically no fever and a reticulocyte response which begins on the third day, after a single injection equivalent to 500 cc. of original volume. We are at present trying to obtain greater potency through refinements in the method of preparation.

Sixty-two intramuscular injections of gastric juice, varying in amounts from 5 cc. to 25 cc., have been given up to the present time (April 27). These have been given deep into the muscles of the buttocks or thighs, either preceded or accompanied by sufficient procain to make a 1 per cent solution. Pain at the site of injection is the most prominent symptom, being present in nearly every case. It is often complained of during the injection but usually develops about 2 hours later, lasting from 6 hours to 4 days, varying a great deal in severity. Occasionally there is some induration of the tissues, but usually the only local reaction is marked tenderness over the area. The temperature has been elevated after about two-thirds of the injections, ranging from 99° to 102° F., appearing from 6 to 12 hours later. Temperatures of 103° and 104° F. have been reached 5 times. Slight chills have occurred twice after intravenous injections and once following an intramuscular injection. Nausea and vomiting occurred after 2 injections in 1 patient and once in each of 2 other patients. Circulatory failure occurred in 1 patient and was relieved by adrenalin. This was probably due to accidental injection into a vein as this patient has received numerous injections since that time without circulatory disturbance. Rather marked flushing of the face and hands was present after 15 of the injections, coming on within 5 minutes after the injection and lasting for 1 to 2 hours. Severe frontal headaches lasting from 2 to 6 hours have occurred 5 times. There has been only slight elevation of the pulse rate following these injections. Since we have been using the acetone extracted swine juice there has been practically no febrile reaction, and the pain has been much less severe and of shorter duration. Flushing of the skin and headache have been noticed only since using the acetone extract.

The anti-anemic substance of gastric juice is thermolabile, dialysable and exhaustible, and is probably a hormone, for which we have proposed the name *addisin*, after Thomas Addison, who first described pernicious anemia. The evidence at hand indicates that this is the physiologic stimulant of the bone marrow which maintains the blood cells and hemoglobin at a normal level.

Conclusion. It seems highly probable that the temporary lack of addisin in the gastric juice is the cause of pernicious anemia. Its administration intramuscularly has proved to be efficacious therapeutically in this disease, and it may be found to be of value in other blood dyscrasias. What effect it may have on the cord changes in pernicious anemia has not been determined.

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REFERENCES.

1. Minot, G. R., and Murphy, W. P.: J. Am. Med. Assn., 1926, 87, 470.
2. Minot, G. R., Cohn, E. J., Murphy, W. P., and Lawson, H. A.: AM. J. MED. SCI., 1928, 175, 599.
3. Sharp, E. A.: J. Am. Med. Assn., 1929, 93, 749.
4. Sturgis, C. C., and Isaacs, R.: J. Am. Med. Assn., 1929, 93, 747.
5. Conner, H. M.: J. Am. Med. Assn., 1930, 93, 338.
6. Wilkinson, J. F.: Brit. Med. J., 1930, 1, 236.
7. Gänsslen, M.: Klin. Wchnschr., 1930, 9, 2099.
8. Castle, W. B., and Taylor, F. H. L.: J. Am. Med. Assn., 1931, 96, 1198.
9. Strauss, M. B., Taylor, F. H. L., and Castle, W. B.: J. Am. Med. Assn., 1931, 97, 313.
10. Castle, W. B., and Locke, E. A.: J. Clin. Invest., 1928, 6, 2.
11. Castle, W. B.: AM. J. MED. SCI., 1929, 178, 748.
12. Castle, W. B., and Townsend, W. C.: AM. J. MED. SCI., 1929, 178, 764.
13. Castle, W. B., Townsend, W. C., and Heath, C. W.: AM. J. MED. SCI., 1930, 180, 305.
14. Castle, W. B., Heath, C. W., and Strauss, M. B.: AM. J. MED. SCI., 1931, 182, 741.
15. Morris, R. S., Schiff, L., Burger, G., and Sherman, J. E.: Cincinnati J. Med., 1932, 13, 27.
16. Morris, R. S., Schiff, L., Burger, G., and Sherman, J. E.: J. Am. Med. Assn., 1932, 98, 1080.
17. Sharp, E. A.: Personal communication.

PERICARDIAL EFFUSION: A CLINICAL STUDY.

BY PAUL D. CAMP, M.D.,

DALTON SCHOLAR, MASSACHUSETTS GENERAL HOSPITAL,

AND

PAUL D. WHITE, M.D.,

PHYSICIAN, MASSACHUSETTS GENERAL HOSPITAL,
BOSTON, MASS.

(From the Cardiac Clinics and Laboratory.)

THE diagnosis of pericardial effusion proven by autopsy has never reached a high degree of accuracy and the low percentage of correct diagnosis is at first thought appalling. When one considers, however, that the normal heart volume displacement is about 750 cc., that it requires a good deal of effusion to add appreciably to this volume, that in a great number of cases in which one finds pericardial effusion one also finds an enlarged heart, and that the effusion is very apt to be a terminal event in a very sick patient, then the diagnostic error is not so glaring.

Historical Review. It is known that the ancients, including Galen, were aware of changes in the pericardium of animals and man. In more modern times Riolan (1646) and Senac (1749) among others described pericarditis with effusion in man. Rondelet and Riverius were able to recognize some of the symptoms of pericardial disease, and their descriptions were added to by Morgagni and others. By the method of immediate percussion Auenbrugger

was able to determine that in some cases of pericardial effusion there was an increase in cardiac dullness, but this observation was put on a much firmer basis by his translator Corvisart, who worked on the subject independently. Laennec is often credited with the discovery of the pericardial friction rub but it seems most certain that the honors should go to his assistants Collin and Devilliers who demonstrated that the friction sound of "creaking leather" was caused by pericarditis.

Pitcairn in 1788 showed the relationship of rheumatism and pericarditis. Since then there have been many etiologic factors discovered and described in the literature, but today as then the rheumatic infection accounts for a large number of cases of pericarditis, perhaps more than any other single etiologic factor.

Pericardial paracentesis was first suggested in 1646 by Riolan; however, this was not actually performed until the year 1819 at which time it was done by Romero of Barcelona. Jowett of Nottingham was the first to use the trocar in doing a pericardial paracentesis. This method was brought into more general repute by Schuh of Vienna in 1839, by Trousseau of France in 1854, and by Allbutt in England in 1866. Thayer and also Shattuck removed by aspiration as much as 1250 cc. a good many years ago. The largest amount of effusion obtained at autopsy was reported by Verney in a case from which he collected 4000 cc. It is interesting to note that in this case pericardial taps had been done on two occasions several days before death, 400 cc. being obtained at one time and 500 cc. at the other. Gibson mentioned a case recorded by Corvisart in which he states that he found 4000 cc. of pericardial fluid.

Experimental work on the pathologic physiology of pericardial effusion was first done by François-Franck in 1877. He demonstrated that, due to its pressure, fluid injected into the pericardial cavity hinders the entrance of blood into the auricles and causes stasis of the blood in the venæ cavæ and a fall in blood pressure. Shortly after this, Lagrolet and Cohnheim experimented with injections of fluid into the pericardium. Starling repeated these experiments and came to the same conclusion as did François-Franck. Many other experiments have been done to attempt to explain the mechanism of pulsus paradoxus, the position assumed by the heart during pericardial effusion, the sites of collection of the fluid within the pericardium, and the physical signs produced by the fluid.

Gauchat and Katz deduce from their experiments with pericardial effusion that the paradoxical pulse is best explained as follows: "With the pericardium distended with fluid, not only is the flow of blood into the heart impeded but the inflow also varies during inspiration and expiration, owing to the fact that the respiratory variations of intrathoracic pressure do not affect the intrapericardial and intracardiac pressures as much as those in the entering veins. This causes a smaller difference of pressure between the veins and

heart during inspiration and allows less filling of each ventricle. Consequently a paradoxical pulse probably appears in both the pulmonary and systemic circuits but obviously the arterial pulsus paradoxus is due to the impaired flow into the left ventricle." Lewis has demonstrated that pulsus paradoxus can easily be produced in a normal person by forced respiration. The mechanism of this is not clear for there is still a decrease of intrathoracic pressure with inspiration and a tendency to an increase of blood flow to the heart. The decreased pressure in the arm artery here is probably not due to any decreased output from the heart, but rather to a compression of the subclavian arteries by the elevation of the chest as the result of increased respiratory effort. Where there is a massive pericardial effusion a marked pulsus paradoxus may occur. The mechanism is probably not wholly like that associated with thoracic breathing without pericarditis, although the thoracic inspiration may still be one factor; the new element of obstruction to the inflow of blood into the heart acts to decrease considerably the size of the pulse in both inspiration and expiration and thus to accentuate the pulsus paradoxus, so that in some cases the pulse may actually disappear during inspiration. However, we have not yet a completely satisfactory explanation for the important sign of the pulsus paradoxus in the presence of considerable pericardial effusion.*

Williamson by injecting a material which hardened after injection concluded as follows from his experiments: (1) In pericardial effusion fluid accumulates first along the lower margin of the heart and about the apex, particularly on the diaphragmatic surface of the heart, and in small effusions this is the only place of regular accumulation. (2) The second place of accumulation is over the great vessels. (3) In at least 14 of 33 cases of pericardial effusion the anterior surface of the heart remained in part uncovered by fluid so that a friction rub could easily exist. This last point is of interest and may explain such cases as reported by Cejka in which a friction rub persisted even when the sac contained 1000 cc. of fluid, and by Porter in which he heard a definite pericardial friction rub just before the aspiration of 1350 cc. of fluid, while a Roentgen ray taken immediately after aspiration showed that only a portion of the fluid was removed.

Cabot stated that with clinical methods not less than 150 cc. of fluid can be recognized. Aporti and Figaroli found no changes in cardiac dullness until about 400 cc. had been injected. Morris and Bader found that at least 500 cc. must be present before it can be detected with the patient in the recumbent position.

Cabot in his book *Facts on the Heart* has reported the results

* Inspiration may act to reduce the inflow of blood into the heart in the presence of extensive pericardial effusion by allowing the pericardial fluid more completely to compress the roots of both vena cava which are elongated and thus more easily collapsed upon descent of the diaphragm.

of his studies of the autopsies at the Massachusetts General Hospital from 1897 to 1919. His findings are briefly as follows: (1) 186 cases of acute pericarditis with or without effusion were found; 141 males, 45 females. (2) Rheumatism in the ordinary sense is only a minor factor in the production of pericarditis. There was a clear rheumatic history in only 12 per cent. (3) Pericarditis is primarily a terminal affair. (4) A friction rub was heard in only 21 per cent of the cases. (5) Sixty-eight of the 186 cases showed 100 cc. or more of exudate: 100 cc. in 7 cases; 150 cc. in 5; 200 cc. in 4; 250 cc. in 1; 200 to 300 cc. in 2; 300 cc. in 4; 300 to 400 cc. in 1; 400 cc. in 1; 500 cc. in 1; 700 cc. in 1; unmeasured in 41. (6) All of these 68 cases, Cabot believes, might have been recognized in life; however, only 7 cases (10 per cent) were so recognized. The Roentgen ray in this early series was rarely used. (7) There was failure to recognize clinically pericarditis either with or without effusion in 77 per cent of the cases. (8) With more frequent use of radioscopy this record should be greatly improved, was Cabot's conclusion.

Present Study. With Cabot's studies in mind, we have conducted the present investigation in order to determine the present status of the diagnosis of pericardial effusion. The material selected for study is composed of three groups: (1) The cases of the general services of the Massachusetts General Hospital in which pericardial fluid of 100 cc. or over was found postmortem, (2) the cases of the Eye and Ear Infirmary of similar nature, and (3) a group of cases in which fluid was obtained by antemortem pericardial paracentesis, thus warranting a diagnosis of pericardial effusion. The material in the above mentioned groups was collected from the records over a ten-year period, from January 1, 1921, to December 31, 1930.

Group I. Postmortem Group of Cases of Pericardial Effusion. There were 95,542 cases admitted and 1729 autopsies performed on the general services of the Massachusetts General Hospital in the 10-year period, 1921 to 1930, inclusive. Of the 1729 autopsies, 126 (7.2 per cent) showed a pericardial effusion of 100 cc. or more. There were 75 males and 51 females; the average age was 43 years and the age incidence by decades was as follows: first 4, second 11, third 21, fourth 25, fifth 15, sixth 22, seventh 22, eighth 5, and ninth 1. The youngest patient was 5 months old and had a purulent pericarditis due to the *Bacillus influenzae* and the pneumococcus; the oldest case of 84 years had a rupture of a dissecting aortic aneurysm into the pericardial sac.

A. CASES WITH 100 TO 250 CC. OF PERICARDIAL FLUID. There were 94 cases, 60 males, 34 females; the average age was 40 years.

1. *Cases without Pericarditis.* There were 72 cases, male 44, female 28; the average age was 42 years.

Etiology. This group presents some very interesting points in etiology.

Twenty-six cases may be classed under the general heading of

chronic passive congestion mostly due to cardiac failure. This subgroup may be further divided as follows: 5 cases associated with definite nephritis without hypertension, 5 cases associated with hypertension but without nephritis, 8 cases with rheumatic heart disease, 2 cases with a question of hypertensive heart disease (in other words, although no definite hypertension was found, it was thought after considering the clinical history that a previous hypertension had existed), 2 cases associated with coronary occlusion, 1 case associated with an extensive chronic pleurisy in which the mechanism of production of the chronic passive congestion was unknown but was probably due to obstruction, and 1 case each associated with subacute bacterial endocarditis, questionable rheumatic heart disease, and arteriosclerosis.

We have classified 24 other cases under the head of infections of various types with a question as to the mechanism of production of the pericardial effusions. In none of these was there a demonstrable pericarditis at necropsy. The subdivision of this group follows: 13 cases associated with lobar pneumonia or bronchopneumonia, 4 cases with empyema or pulmonary abscess, 3 cases with streptococcus infection, 1 case of *Bacillus coli* infection and 3 cases of infection in which the infecting organism was not found.

Three other cases were diagnosed clinically and at autopsy as chronic passive congestion but no pleural effusions were found in them. This brings up the question as to whether or not fluid may collect in the pericardial sac and not also in the pleural cavities in cases of chronic passive congestion. These 3 cases were associated with the following: (1) chronic rheumatic heart with subacute bacterial endocarditis, (2) pernicious anemia, (3) nephritis and hypertension.

There are 2 cases associated with nutritional edema and 1 case with the nephritic edema of Fahr.

We found 8 other cases associated with malignancy not involving the pericardium.

An additional case presented chronic rheumatic heart disease with acute pulmonary edema; the pericardial as well as pleural fluid was bloody and we thought of the possibility of rupture of engorged vessels as a cause of this effusion. The remaining 7 cases of this group were associated with conditions in which the mechanism of the collection of the fluid was entirely unknown and were composed as follows: 2 cases of miliary tuberculosis (without pericardial involvement); 1 case of lues; 1 case of lues and tuberculosis combined; 1 case of myxedema; 1 case of unknown cause with a questionable diagnosis of lues and Ayerza's disease; and 1 case of cirrhosis of the liver.

The type of pericardial fluid in these 72 cases was as follows: clear, 54; "amber," 14; turbid, 1; serosanguineous, 1; bloody, 2.

Pleural effusions of 500 cc. or over were found in 32 of these 72 cases, and of less amount in 15 others; the fluid was clear in 27 cases, turbid in 11, bloody in 6, and purulent in 3.

Symptoms. Precordial pain was present in 12 cases and absent or not mentioned in 60 cases. Dyspnea was present in 38 cases and absent in 34 cases.

Signs. A definite pericardial friction rub was not mentioned in any of this group; it was questioned on 2 occasions, noted as absent in 2 cases, and not mentioned in the remainder. Murmurs were present in 33 cases.

Heart Weights. The heart weight was recorded in 67 of the 72 cases; it was less than 300 gm. in 15 cases, 300 to 500 gm. in 30 cases, and over 500 gm. in 22 cases.

Electrocardiograms. These were not very enlightening and the classifications as given necessarily overlap. We found the following in 12 of the 72 cases electrocardiographed; normal rhythm, 6 cases; partial auriculoventricular block, 4 cases; premature beats, 2 cases.

Radiographic Examination. A correct Roentgen ray diagnosis was not made in any of 26 instances examined by Roentgen ray; the diagnosis of pericardial effusion was questioned 3 times and missed in the other 23 patients.

Clinical Diagnosis. Not one of the 72 cases was diagnosed as pericardial effusion; the diagnosis was questioned in 1 case which was seen by the medical service. The medical service alone examined 34 cases, the surgical service alone examined 5 cases, the pediatric service alone 1 case and cardiac consultants examined 16 cases. The remaining 16 cases were seen by the general services together, mostly the medical service in consultation with the surgical. The conditions of the patients were as follows: acutely ill, 33; moribund, 11; chronically ill, 24; died suddenly, 4.

2. *Cases with Pericarditis.* This group was composed of 21 cases, 15 males and 6 females; the average age was 42 years.

Etiology. The pericarditis was due to several types of infection or uremia as follows: pneumococcus Type II, 1; Bacillus influenzae and pneumococcus, 1; pneumonia without specified organism, 2; Staphylococcus aureus, 2; streptococcus, 4; purulent lung infections, 2; acute rheumatic heart disease, 4; subacute bacterial endocarditis, 1; infection associated with lues, 2; and uremia, 2.

The character of the pericardial fluid was found to be as follows: serofibrinous, 9 cases; turbid, 1; serosanguineous, 1; bloody, 1; and purulent, 9.

Pleural effusions of 500 cc. or over were found in 9 cases, of less amount in 7 cases, and no pleural effusions were noted in 5 cases. The fluid was clear in 7 cases, turbid in 2, and purulent in 7.

Symptoms. Dyspnea was present in 9 cases, and absent or not mentioned in 12 cases. Precordial pain was noted in only 2 cases.

Signs. A pericardial friction rub was heard in 3 cases. Murmurs were present in 12 cases.

Heart Weights. Hearts weighing less than 300 gm. were found in 6 cases, 300 to 500 gm. in 8, and over 500 gm. in 4; the weights were not recorded in the remaining 3 cases.

Electrocardiograms. Electrocardiograms were taken in only 2 cases, 1 of which showed normal rhythm and the other auricular fibrillation. Neither record showed low voltage.

Radiographic Examination. A Roentgen ray diagnosis of pericardial effusion was correctly made in 1 case; in the other 7 cases examined by Roentgen ray a pericardial effusion was not diagnosed once.

Clinical Diagnosis. Of the 21 cases in this group, 4 were correctly diagnosed clinically. The medical service alone examined 7 cases and made a correct diagnosis once; the surgical service alone examined 5 cases and also made one correct diagnosis; the pediatric service examined 1 case without correct diagnosis; the medical and surgical services combined saw 3 cases and failed to make the diagnosis in any of them; cardiac consultants saw 5 cases and diagnosed 2 of these correctly. Twelve of the 21 patients were acutely ill, 1 moribund, 1 died suddenly, and 7 were chronically ill.

3. *With New Growth Involving the Pericardium.* In this group there was 1 case, a male aged 36 years. His pericardial fluid was of amber color. Pleural fluid was present, over 500 cc. in amount and bloody. Pain and dyspnea were absent. A friction rub was not mentioned, but there was an apical systolic murmur. The heart weighed less than 300 gm. An electrocardiogram was not obtained. The Roentgen ray diagnosis of pericardial effusion was not made nor was the correct clinical diagnosis made. The patient was chronically ill.

Summary of Class A. Cases with 100 to 250 cc. of Pericardial Fluid. There were 94 cases in this group, 60 males and 34 females, the average age being 40 years. Twenty-one cases showed a pericarditis, 72 cases did not have a demonstrable pericarditis, and there was 1 case of new growth involving the pericardium by metastasis. In the group with pericarditis the etiologic factor was infection of some type in all except 2 cases which were associated with uremia; in the group without pericarditis chronic passive congestion was the most important factor while infections of various types but not involving the pericardium in a demonstrable way account for the next largest group; the remainder were associated with miscellaneous diseases such as malignancy, tuberculosis, nutritional edema, lues, and acute pulmonary edema. The pericardial as well as pleural effusions varied according to the nature of the etiologic agent. Dyspnea was present in 47 cases; pain was noted in 14 cases. Friction rubs were heard in only 3 cases. Murmurs were heard in 46 cases. The orthopneic position was assumed by

25 patients. Cervical veins were noted as distended in only 2 cases and heart sounds were noted as distant in 21 cases. A pulsus paradoxus was not recorded in any case. The electrocardiograms were not significant. A correct Roentgen ray diagnosis was made in 1 case, and questioned in 3 of the 35 cases examined. A correct clinical diagnosis was made in 4 and questioned in 1 other of the total of 94 cases.

B. CASES WITH 250 TO 500 CC. OF PERICARDIAL EFFUSION. 1. *Cases without Pericarditis.* Twenty belong in this group; 13 males and 7 females.

Etiology. Here again we found that the largest etiologic factor was chronic passive congestion due to heart failure. There were 11 such cases, associated as follows: with hypertension in 1 case, questionable hypertension in 3, nephritis and hypertension in 1, calcareous valvular heart disease in 1, chronic rheumatic heart disease in 4, and bronchopneumonia in 1. There were 4 cases of myocardial infarction and 1 case each of the following: ruptured aortic aneurysm, myelogenous leukemia, tuberculosis associated with Hodgkin's disease, and subacute bacterial endocarditis due to infection with the *Streptococcus viridans*.

The pericardial fluid was clear in 16 of the 20 cases, "amber" in 2, and bloody in 2.

Pleural effusions were noted in 13 cases, being over 500 cc. in amount in 9 of these. The pleural fluid was clear or turbid in 8 of these 13 cases, bloody in 4, and purulent in 1.

Symptoms. Six cases showed precordial pain. Dyspnea was present in 16 cases and absent in 4.

Signs. A pericardial friction rub was questioned in 1 case and not mentioned and apparently absent in the remaining 19. Murmurs were present in 13 cases and noted as absent in 7 cases.

Heart Weights. Of the weights recorded in 18 cases we found the following: less than 300 gm., 2 cases; 300 to 500 gm, 6 cases; over 500 gm., 10 cases.

Electrocardiograms. Electrocardiograms were taken in 3 cases which showed, respectively, the following points of interest: (1) inverted T₂ and left axis deviation; (2) partial auriculoventricular block with P-R interval of 0.22 second and also intraventricular block; (3) left axis deviation and auricular and ventricular premature beats. Low voltage was not present in these 3 cases.

Radiographic Examination. A correct Roentgen ray diagnosis was not made, but was questioned once, in the 6 cases examined.

Clinical Diagnosis. In none of this group was a clinical diagnosis of pericardial effusion made, but in 1 case examined by the medical service this diagnosis was questioned. The medical service alone examined 14 cases, the surgical alone and the medical and surgical combined saw 1 case each, and the cardiac consultants examined 4 cases. The conditions of the patients were as follows:

acutely ill, 5; chronically ill, 5; intermediate, 10; 2 cases were moribund and 3 cases died suddenly.

2. *Cases with Pericarditis.* Only 2 cases occurred in this group; both were females.

Etiology. Nephritis was present in 1 case; an infection by undetermined organism existed in both.

The *pericardial fluid* was serofibrinous in both cases.

One had over 500 cc. of *pleural effusion* and the other less; the pleural fluid was purulent in both.

Symptoms. Both pain and dyspnea were present in 1 case but were absent in the other.

Signs. A pericardial friction rub was present in both cases. A murmur was present in 1 and absent in the other.

The *heart weight* was recorded in 1 case as between 300 and 500 gm.

Radiographic Examination. Only 1 case was examined and the correct diagnosis was questioned in this instance.

Electrocardiogram. The 1 case examined electrocardiographically showed ventricular premature beats and a diphasic *T* wave in Lead 2; the voltage was not low.

Clinical Diagnosis. The medical service examined these 2 cases; 1 was moribund and 1 chronically ill; the clinical diagnosis of pericardial effusion was not made in either case.

3. *New Growth Involving the Pericardium.* There were 2 cases in this group of malignancies of the pericardium; 1 male, and 1 female.

The *pericardial fluid* was clear in 1 case and bloody in the other. One case contained less than 500 cc. of purulent pleural fluid.

Symptoms. Dyspnea was present and pain was absent in both cases.

Signs. A pericardial friction rub was not mentioned in either case; 1 case had a murmur and the other did not.

The *heart weight* was recorded in 1 case as between 300 and 500 gm.

Electrocardiograms were not done.

A correct *Roentgen ray diagnosis* was not made in either case.

Clinical Diagnosis. One case was examined by the cardiac consultants and 1 by the medical and surgical service combined; a clinical diagnosis of pericardial effusion was not made in either case. One patient was acutely ill, the other moribund.

Summary of Class B. Cases with 250 to 500 cc. of Pericardial Effusion. This group contained 24 cases altogether: 15 males and 9 females. Twenty cases showed no pericarditis, while there were 2 cases each of pericarditis and of malignancy involving the pericardium. In the group without pericarditis chronic passive congestion was found to be the main etiologic factor, cardiac infarction was next in importance, and the remaining cases presented a variety of diseases. In the 2 cases with pericarditis nephritis was present in 1, and in both cases an undetermined organism was responsible

for infection elsewhere in the body. The pericardial fluid varied according to the type of disease. Pain was present in 7 cases and dyspnea in 18 cases. A pericardial friction rub was heard twice and questioned once. Heart sounds were noted as distant in 6 cases. A pulsus paradoxus was not recorded in any case. The cervical veins were distended in 3 cases but this finding may have been due to the congestive heart failure. Ten patients out of the 24 elected the orthopneic position. The electrocardiograms were not significant. Of 9 patients examined by Roentgen ray 8 were not diagnosed as pericardial effusion; the diagnosis was questioned once. Clinically the diagnosis of pericardial effusion was not definitely made in any case; it was questioned on only one occasion.

C. CASES WITH OVER 500 CC. OF PERICARDIAL EFFUSION. 1. *Cases without Pericarditis.* There were 5 cases with over 500 cc. in this group: 2 males and 3 females.

Etiology. The etiological factor was as follows: chronic passive congestion in 3 cases (1 case each associated with subacute bacterial endocarditis, questionable rheumatic heart disease and infection with the Streptococcus hemolyticus, and myxedema), tuberculosis in 1 case associated with doubtful chronic passive congestion, and, finally, unknown mechanism in 1 case of heart disease.

The *pericardial fluid* was clear in 3 cases and bloody in 2.

Four cases had *pleural effusions* of over 500 cc.; in 3 of these the pleural fluid was clear and in 1 bloody.

Symptoms. Pain was absent in all 5 cases. Dyspnea present in 2.

Signs. A pericardial friction rub was recorded as present in 1 case and not mentioned in 4 cases. Murmurs were present in all 5 cases.

Heart Weights. The heart in 1 case weighed less than 300 gm., in 4 cases it weighed over 500 gm.

Electrocardiograms were done on 3 cases, 2 of which showed low voltage; the other 1 showed diphasic *T* waves in Leads 1 and 2.

Radiographic Examination. Of 4 cases examined by Roentgen ray the diagnosis of pericardial effusion was questioned once and not noted in the other 3.

Clinical Diagnosis. The medical service examined 3 cases but did not diagnose pericardial effusion. The cardiac consultants examined 2 cases and made the correct diagnosis once.

2. *Cases with Pericarditis.* Only 1 case occurred in this group. It was an instance of polyserositis in a woman aged 21 years.

The *pericardial fluid* was serosanguineous.

There was a *pleural effusion* of over 500 cc. which was turbid.

Symptoms. Pain and dyspnea were both present in this patient.

Signs. A pericardial friction rub was present in addition to a systolic apical heart murmur.

The *electrocardiogram* showed low *T* waves in all leads and small complexes.

In a *radiographic examination* the diagnosis of pericardial effusion was questioned.

A cardiac consultant saw this patient in consultation with the medical service; the correct clinical diagnosis was made. The patient was chronically ill.

3. *Malignancy Involving the Pericardium.* There were 2 males in this group of malignancy secondarily involving the pericardium.

Bloody pericardial effusion was found in both.

There was a clear *pleural effusion* in both cases, 1 of more than 500 cc.

Symptoms. Pain and dyspnea were present in these 2 cases.

Signs. A pericardial friction rub was noted as absent in 1 case and not mentioned in the other. Murmurs were not heard.

In the 1 case examined by *Roentgen ray* a pericardial effusion was not diagnosed.

Both of these cases were seen by the medical and surgical services together; a diagnosis of pericardial effusion was not made. The patients were chronically ill.

Summary of Class C. Cases with 500 cc. or More of Pericardial Effusion. We found in this group 8 cases, 4 males and 4 females. In only 1 case did pericarditis occur; 2 cases had malignant disease involving the pericardium. Five cases had no pericarditis and of these 5 cases 3 had chronic passive congestion; in the other 2 the mechanism of the production of the pericardial fluid was not evident. The pericarditis was associated with polyserositis in 1 case. The pericardial fluid was serosanguineous or bloody in 4 cases and clear in 4. Pain was present in 3 cases and dyspnea in 2. The orthopneic position was noted in 2 patients but there was no statement of distention of the cervical veins. Heart sounds were recorded as distant in 2 cases. The presence or absence of the *pulsus paradoxus* was not noted. The electrocardiograms in this group showed a constant tendency to small complexes. Of the 5 cases examined by *Roentgen ray* the diagnosis of pericardial effusion was not made positively in any; it was questioned in 1 case. The correct clinical diagnosis was made in 2 cases, 1 with and 1 without pericarditis.

D. SIX CASES OF THE POSTMORTEM SERIES OF PERICARDIAL EFFUSION CORRECTLY DIAGNOSED CLINICALLY. 1. *Cases with 100 to 250 cc. of Pericardial Fluid.* Four cases occurred in this group, 3 males and 1 female; the average age was 37 years.

Etiology. All 4 cases had pericarditis, due in 2 to acute rheumatism and in the remaining 2 to other acute infection, *Staphylococcus aureus* in 1 and an undetermined organism in the other.

The *character of the pericardial fluid* was as follows: serofibrinous in 2 cases, bloody in 1, and purulent in 1.

Two cases had *pleural effusions* of over 500 cc. and 1 had less than that amount; the pleural fluid was clear in 2 cases and turbid in 1 case.

Symptoms. Pain was present in 1 case; dyspnea was present in all 4 cases.

Signs. A pericardial friction rub was noted as present in 2 cases and absent in 1. Heart sounds were distant in 2 instances. The pulsus paradoxus was present in 1 case during an operation of pericardiotomy but disappeared about 12 hours later; it was not noted before the operation. The cervical veins were distended in 1 case, and 3 patients assumed the orthopneic position.

An *electrocardiogram* was done in 1 case with acute rheumatic pericarditis; it showed sinus arrhythmia and bradycardia, with poorly marked *P* waves and intraventricular block.

A correct Roentgen ray diagnosis was made in 1 out of 3 cases examined.

Pericardial paracentesis was attempted in 2 of these 4 patients. One case yielded 32 cc. of purulent fluid and, when a pericardiotomy was performed later, about 50 cc. of *Staphylococcus aureus* pus was removed. Several taps were tried in different locations on the other patient but only 5 cc. of blood were obtained. It is interesting to note that in this case on postmortem examination the fluid was found to be encapsulated.

2. *Cases with 250 to 500 cc. of Pericardial Fluid.* There were no cases in this group diagnosed correctly before death.

3. *Cases with Over 500 cc. of Pericardial Fluid.* There were 2 cases in this group.

One case was a woman aged 21 years with polyserositis. The pericardial fluid of 800 cc. was purulent. There was also a pleural effusion of 500 cc. in amount; this pleural fluid was turbid. Both pain and dyspnea were present in this case. A pericardial friction rub was present. The character of the heart sounds was good; systolic and diastolic murmurs were heard at the base of the heart. Neither pulsus paradoxus, nor condition of cervical veins, nor position of the patient was mentioned in the record. The electrocardiogram presented rather low *T* waves and small complexes in all leads. The Roentgen ray report stated that there was no positive evidence of fluid in the pericardium.

The other case was one without pericarditis in a man, aged 32 years. The etiologic factor was chronic passive congestion associated with subacute bacterial endocarditis. Five hundred cc. of clear fluid were found in the pericardial sac and 1500 cc. of clear fluid were noted in the pleural cavities. Pain and dyspnea were absent. A pericardial friction rub and the pulsus paradoxus were recorded as absent. The condition of the cervical veins and the position of the patient were not noted. Roentgen ray and electrocardiographic examinations were not done.

Summary of Group D. Six Cases of the Postmortem Series of Pericardial Effusions Correctly Diagnosed Clinically. Of these 6 cases correctly diagnosed there were 4 males and 2 females. Four of the

cases contained 100 to 250 cc. of fluid in the pericardial sac and pericarditis was present in each instance. There were 2 cases with 500 cc. or more of fluid; 1 of these cases had pericarditis while the other did not. Two cases had acute rheumatic pericarditis, 2 cases pericarditis associated with infection, 1 had polyserositis and 1 had chronic passive congestion. Four cases had over 500 cc. of pleural effusion, which was clear or slightly turbid in all cases. The pericardial fluid was as follows: bloody, 2; purulent, 2; serofibrinous, 1; and clear, 1. Pain was present in 2 cases, and dyspnea in 5. A pericardial friction rub was heard in 3 cases. The pulsus paradoxus was noted once and 3 patients assumed the orthopneic position; the cervical veins were noted as distended in only 1 instance. Heart sounds were poor or distant in 2 cases; murmurs were present in all cases. The electrocardiogram of the 1 case with more than 500 cc. of pericardial fluid was interesting in that it showed low voltage. Correct Roentgen ray diagnosis was made in 1 of the 3 cases having 100 to 250 cc. of pericardial fluid; it was questioned in the 1 case with over 500 cc. which was radiographed. Three of the patients were acutely ill and 3 were chronically ill.

E. CASES OF PERICARDIAL EFFUSION FROM EYE AND EAR SERVICE. This small group is composed of 1 female, 72 years of age, and 1 male, 23 years of age. The former had a streptococcus pericarditis associated with otitis media; the latter had a streptococcus pericarditis associated with mediastinitis and laryngeal edema. In the former case there were 100 cc. of purulent fluid and in the latter 200 cc. of serofibrinous fluid. Pain was present in the latter case. The presence or absence of dyspnea was not noted. There was no mention of any of the following signs: position of patient, murmurs, cervical veins, heart sounds, pulsus paradoxus. A pericardial friction rub was noted as present in the latter case but not mentioned in the former. The Roentgen ray report on the latter case in which were found 200 cc. of fluid was as follows: "Very broad superior mediastinum." The clinical diagnosis of effusion was not made in either case. In the case which had 200 cc. of fluid the diagnosis of "Pericarditis" was made but the opinion offered regarding effusion was: "No signs of effusion." Both patients were acutely ill and medical consultants saw both of them.

Group II. Pericardial Paracentesis Cases of Pericardial Effusion Without Postmortem Examination. This group is composed of 15 clinical cases with the diagnosis of pericardial effusion definitely established by the removal of fluid from the pericardium, either by a simple paracentesis with trocar or by more complicated operations. Twelve of these cases were taken from the records of the general services of the Massachusetts General Hospital and represent the number of such cases from January 1, 1920, to February 1, 1931. Three of the cases were taken from our private case records.

There were 14 males and 1 female. The youngest was 9 months old and the oldest 46 years. The ages by decades were as follows: first, 4; second, 4; third, 2; fourth, 4; and fifth, 1.

Etiology. Five of the 15 cases had acute rheumatic pericarditis, 2 had tuberculosis of the pericardium, and there was 1 case each of the following: questionable rheumatic pericarditis, Streptococcus viridans endocarditis complicating rheumatic heart disease, Staphylococcus aureus infection with osteomyelitis, Streptococcus hemolyticus infection, pneumococcus infection Type I, postscarlatinal infection, purulent pericarditis due to an unknown organism, and probable polyserositis.

Pericardial Fluid. The amounts removed by tapping were as follows: less than 100 cc. in 3 cases, 100 to 250 cc. in 5; 250 to 500 cc. in 2, and 500 cc. or over in 5. In 1 of these last 5 cases in which there was a constant drainage tube inserted the exact amount drawn off was not known but by means of a postmortem paracentesis 650 cc. were obtained. The character of the fluid in the 15 cases was as follows: clear, 1; "amber," 4; serofibrinous, 2; serosanguineous, 1; bloody, 2; turbid, 2, and purulent, 3.

Symptoms. Pain was present in 9 cases and noted as absent in 2. Dyspnea was present in 13 cases and absent in 2.

Signs. Pericardial friction rubs were heard in 12 cases and noted as absent in 1 case. Ten cases presented murmurs; 5 had no murmurs. The heart sounds were distant in 11 cases, fair in 3, and good in 1. A pulsus paradoxus was noted as present in 8 cases. The cervical veins were noted as distended in 4 and normal in 1, whereas 9 patients were in the orthopneic position and 2 were able to lie flat.

Radiographic Examination. Thirteen of the 15 cases were examined by Roentgen ray. A correct diagnosis was made in 12 cases and the diagnosis of pericardial effusion was questioned in the other case.

Electrocardiograms were done in 3 of these patients but showed nothing of value in helping to confirm or to deny the diagnosis of effusion.

Course. Seven cases died while under close observation; 8 cases were discharged improved but 1 of these died suddenly soon after. One of the cases has since returned to the hospital and is included as 1 of the 2 cases on which a cardiolysis was done. Microscopic sections of the pericardium in this case are suggestive of tuberculosis.

One of the most interesting and instructive points in this group was that 650 cc. of fluid were obtained by paracentesis in 1 case immediately after the patient died. In this case on previous paracentesis only a small amount of fluid was obtained, which makes us believe that the other cases also had much larger amounts of fluid than were obtained on tapping the pericardium, and in fact a much

larger amount of fluid than is usually stated to be necessary to produce signs and symptoms sufficient to establish the clinical diagnosis of pericardial effusion.

The case which presented a combination of constricting pericarditis and pericardial effusion calls our attention to the problem from a somewhat different angle. Here the amount of fluid found in the pericardial sac was not of great quantity (Fig. 1) and yet the patient showed marked signs and symptoms of cardiac embarrassment due to extrinsic factors and, as the pericardium was definitely thickened and acted as a constrictor of the heart, we may assume that this factor rather than the fluid was the cause of the signs and symptoms in this patient.

Clinical Diagnosis. The correct clinical diagnosis was made in all of the 15 cases.

Treatment. Therapy in these cases of pericardial effusion consisted in the first place of paracentesis, often with considerable relief. Sometimes the tapping was repeated. Almost always as much fluid as possible was withdrawn, without harmful effects. Otherwise symptomatic therapy was carried out as needed, with salicylate treatment in the rheumatic cases and a recommendation for sanitarium treatment in the case of the tuberculous patients. Cardiolysis was done in 2 cases and a pericardiotomy in 2 others. Oxygen was injected into the pericardium in 1 case after fluid was removed (Figs. 2 and 3) and this procedure was repeated three times over an interval of 2 months. From 200 to 600 cc. of oxygen were introduced each time after a larger amount of fluid was withdrawn. In spite of this procedure the pericardium later contracted and had to be resected at operation 5 months later. Perhaps the procedure of therapeutic pneumopericardium was not continued sufficiently long in this case—an interval of 6 to 12 months might have proved more successful.*

Summary. We have presented herewith (1) the pertinent clinical and pathologic data on the 126 cases containing over 100 cc. of pericardial fluid found at postmortem examination at the Massachusetts General Hospital over a period of 10 years (1921 to 1930, inclusive), this number occurring among 95,542 cases admitted to the hospital and among 1729 necropsies (7.3 per cent); (2) similar data collected from the Massachusetts Eye and Ear Infirmary, in a series of 71,334 admissions and 109 necropsies, 2 cases (1.83 per cent) showing 100 cc. or more of pericardial fluid; and (3) the clinical data on 15 cases in which pericardial paracentesis established the diagnosis of pericardial effusion.

I. The postmortem group was divided into (A) cases with 100 to 250 cc. of pericardial fluid, (B) cases with 250 to 500 cc., and (C)

* The individual case reports which have been omitted here for the sake of brevity are included in the authors' reprints.

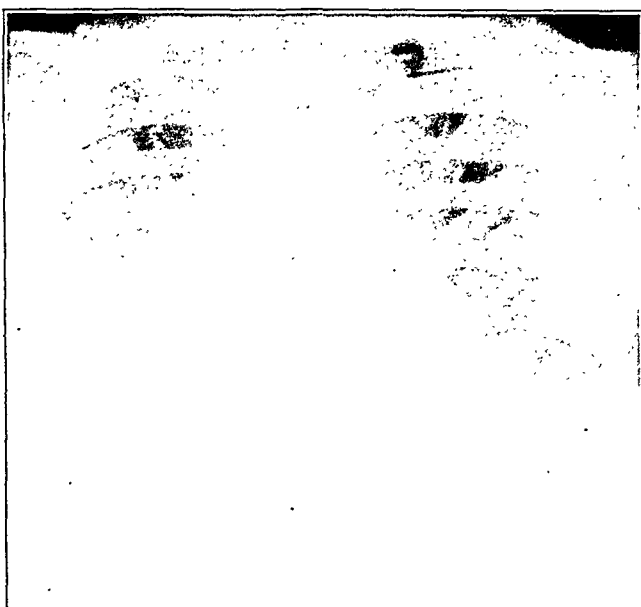


FIG. 1.—Roentgen ray picture of heart and pericardial shadow of J. B., Case 14 of the pericardial paracentesis cases. In this case there was a small pericardial effusion restricted in amount by a much thickened constricting pericardium (proved at operation). There was also fluid in both pleural cavities. Tuberculous pericarditis.

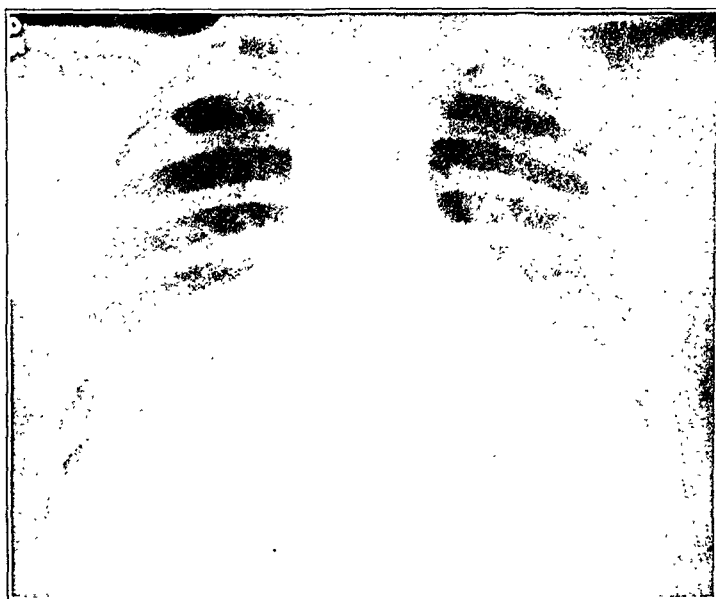


FIG. 2.—Roentgen ray picture of the enormous pericardial effusion of L. A., Case 15 of the pericardial paracentesis cases. Tuberculous pericarditis.



FIG. 3.—Roentgen ray picture, showing oxygen and fluid in the pericardium of L. A., Case 15, whose pericardial effusion before paracentesis was shown in Fig. 2. The oxygen was introduced as a therapeutic procedure.

cases with 500 cc. and over. These were subdivided into cases with pericarditis, without pericarditis, and with new growth. Class A contained 94 cases: 72 without pericarditis, 21 with pericarditis, and 1 with new growth. Class B contained 24 cases: 20 without pericarditis, 2 with pericarditis, and 2 with new growth. Class C contained 8 cases: 5 without pericarditis, 1 with pericarditis, and 2 with new growth. There were 2 cases from the Eye and Ear Infirmary, both of which had pericarditis and less than 250 cc. of fluid.

Etiology. The predominant etiologic factor in the cases with pericarditis was infection of some type (uremia was a rare cause). In cases without pericarditis the predominant etiologic factor was chronic passive congestion or infection elsewhere in the body, with some question as to the mechanism of the production of the pericardial effusion.

Symptoms and Signs. Pain was present in 24 of the 126 cases of the postmortem series of the Massachusetts General Hospital, dyspnea in 68, orthopnea in 37, distended cervical veins were noted in 5; pericardial friction rub in 8, distant heart sounds in 29, and the pulsus paradoxus in 1 case.

Radiography. Forty-nine cases were examined by Roentgen ray. A correct diagnosis was made once and questioned in 3 other cases. Allowances must be made because many of these cases were examined at least several days before death and often in a very sick condition, with pleural fluid sometimes obscuring a part of the heart shadow.

Clinical Diagnosis. Of the 126 cases of the postmortem series at the Massachusetts General Hospital a correct clinical diagnosis was made only six times. Four of these 6 had pericarditis with an effusion of 100 to 250 cc. Two had an effusion of over 500 cc., 1 with and 1 without pericarditis. The diagnosis of effusion was questioned in 1 case with 100 to 250 cc. without pericarditis. Here again the same allowances must be made as in the case of the Roentgen ray diagnosis just cited.

II. The clinical group of 15 other cases in whom a pericardial paracentesis established the diagnosis of pericardial effusion was most instructive since it was made up of patients who presented the classical signs of effusion in a much greater degree than did the "postmortem" cases.

From 1 of these cases 650 cc. of fluid were obtained by a pericardial paracentesis immediately postmortem, while during life paracentesis had yielded a much smaller amount. Since this case presented signs and symptoms similar to the others in this group and since even larger amounts of fluid were obtained in others we believe that almost every one of these clinical cases had over 500 cc. of pericardial fluid.

Another interesting case in this group was that one in which there was a chronic constrictive tuberculous pericarditis to which was added an acute or subacute pericardial effusion. Here the amount of fluid was small but it was sufficient when added to the already constricted pericardial sac to cause grave clinical signs and symptoms.

Conclusions. From the above data we conclude that without the presence of an acute fibrinous pericarditis, the diagnosis of pericardial fluid is likely to be missed unless the effusion amounts to over 500 cc.

To establish a clinical diagnosis of a pericardial effusion all signs and symptoms must be very carefully looked for and analyzed and Roentgen ray studies employed in all cases except a very few where the effusion is so large and rapid in its development that the clinical diagnosis is easily made at once.

REFERENCES.

Historical data concerning Galen, Senac, Rondelet, Riverius, Morgagni, Auenbrugger, Corvisart, Riolan, Schuh, Trousseau, Allbutt and Cejka, quoted from G. H. Gibson: *Diseases of the Heart and Aorta*, Edinburgh and London, 1898.

Cabot, R. C.: *Facts on the Heart*, Philadelphia, W. B. Saunders Company, 1928.
Cohnheim, J.: *Vorlesungen über allgemeine Pathologie*, Berlin, 1822. Quoted from Hirschfelder, A. D.: *Diseases of the Heart and Aorta*, London, Lippincott, 1918.

Collin: *Les diverses méthodes d'exploration de la poitrine*, Paris, 1824, pp. 60, 64.

Coxe, J. R.: *The Writings of Hippocrates and Galen Epitomized from the original Latin translations*, Philadelphia, Lindsay and Blakiston, 1816.

François-Franck, A.: *Recherches sur la mode de production des troubles circulatoires dans les épanchements abondants du péricarde*, *Gaz. hebdomadaire de médecine*, Paris, 1877.

Gauchat, H. W., and Katz, L. N.: *Observations in Pulsus Paradoxus (with Special Reference to Pericardial Effusions): I. Clinical; II. Experimental*, *Arch. Int. Med.*, 1924, **33**, 350, 371.

Gibson, G. H.: *Diseases of the Heart and Aorta*, Edinburgh and London, 1898.
Jowett, quoted from Hirschfelder, A. D.: *Diseases of the Heart and Aorta*, London, Lippincott, 1918.

Lewis, T.: *Studies of the Relationship Between Respiration and Blood Pressure: Part II. Facts Bearing on the Relationship of Different Factors in the Production of Respiratory Curves of Blood Pressure*, *J. Physiol.*, 1908, **37**, 233.

Morris, R. A., and Bader, E. R.: *A Comparison of the Percussion and Roentgen Ray Findings After Injection of the Pericardium*, *J. Am. Med. Assn.*, 1917, **69**, 450. Aporti and Figaruti are quoted in this article.

Pitcairn, mentioned in Baillie: *Morbid Anatomy*, 2d ed., London, 1797, p. 46.

Porter, W. B.: *Pericarditis with Effusion*, *Virginia Med. Month.*, 1922, **49**, 140.

Romero, mentioned by Mirat: *Dictionnaire des Sciences médicales*, Paris, 1819.

Sagrolet: *De la compression du cœur dans les épanchements du péricarde*, Thèse, Paris, 1808.

Shattuck, F. C.: *Pericarditis: Some Points in Its Diagnosis and Treatment*, *Trans. Assn. Am. Phys.*, 1897, **12**, 185; *Boston Med. and Surg. J.*, 1897, **137**, 28.

Starling, E. H.: *Some Points in the Pathology of Heart Disease*, *Lancet*, 1897, **1**, 569, 723.

Thayer, W. S.: *Observations in Two Cases of Tuberculous Pericarditis With Effusion*, *Bull. Johns Hopkins Hosp.*, 1904, **15**, 149.

Verney: *Sur la ponction du péricarde*, *Gaz. hebdomadaire de médecine et de chirurgie*, Paris, 1856, **3**, 793.

Williamson, C. A.: *Pericarditis With Effusion: An Experimental Study*, *Arch. Int. Med.*, 1920, **25**, 206.

NONFATAL STAB WOUNDS OF THE VENTRICLES.

WITH ELECTROCARDIOGRAPHIC SIGNS OF CORONARY THROMBOSIS
AND ABSENCE OF ANGINAL PAIN.*

BY WILLIAM B. PORTER, M.D.,

PROFESSOR OF MEDICINE,

AND

ISAAC A. BIGGER, M.D.,

PROFESSOR OF SURGERY,

MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VA.

WOUNDS of the ventricular musculature with and without injury to one of the major branches of the coronary arteries have been reported in considerable numbers in current medical literature. The electrocardiographic changes noted by observers using this method of study have been similar in essential details to those seen in acute coronary thrombosis. It has been our good fortune to have for study 2 patients with stab wounds of the ventricles, 1 involving the left ventricular musculature and a branch of the left coronary artery and the other the right ventricular musculature, but with no injury to a coronary vessel. Both patients were treated surgically and each patient has been followed sufficiently long to note his complete clinical recovery.

The electrocardiograms are of interest in that the changes are marked and are produced by lesions, the location and extent of which are definitely known. It is reasonable to assume that the heart muscles were normal before the accident, for neither patient gave a history indicating any previous disease liable to produce heart muscle pathology, and their youth and general physical survey precluded the existence of any degenerative vascular disease.

In 1 instance a coronary artery was tied and in both instances muscle tissue was enmeshed by suture material producing a lesion somewhat similar in character to a small myocardial infarction. In each instance the operation was performed under local anesthesia which permitted accurate notation of subjective phenomena. It is of peculiar interest to note that in neither case was pain of an anginal type noted during or following the procedure.

This report is presented not only to place on record wounds of the heart treated surgically with recovery, but particularly to record the clinical behavior of the patients, noting the absence of pain in heart lesions with electrocardiographic changes similar to those

* Read at the Meeting of the American Climatological and Clinical Association, Atlantic City, May 5, 1932.

observed in coronary occlusions and produced probably by myocardial changes of the same fundamental nature.

Case Reports.* CASE 1.—W. R., negro, male, aged 23 years, was admitted to the St. Philip Hospital, October 2, 1930, at noon. He had been stabbed in the left side of the chest about thirty minutes before admission. He later stated that he walked $1\frac{1}{2}$ blocks after being stabbed before he began to feel faint, and estimated that 10 to 15 minutes elapsed

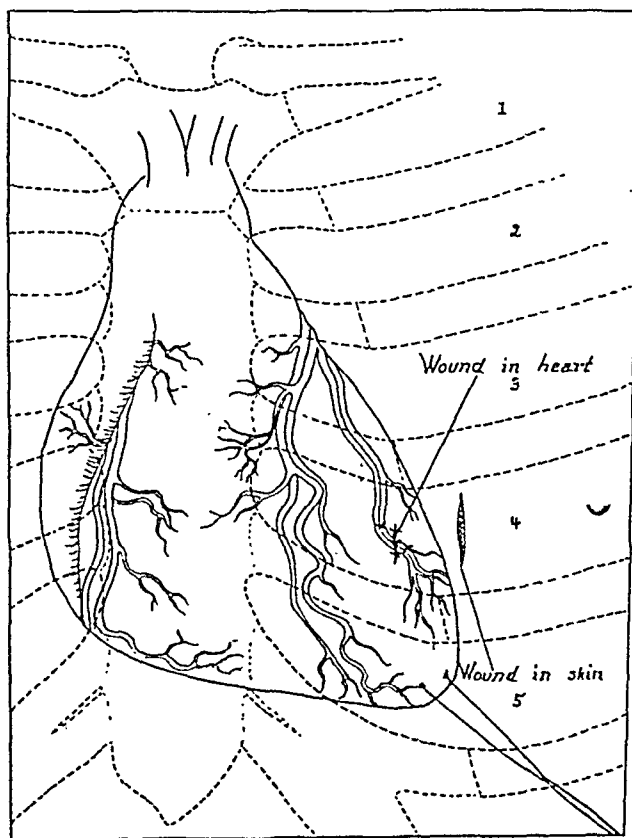


FIG. 1.—Case 1. The approximate location and size of the wound in the left ventricle and the severed coronary vessel.

between the time of injury and the appearance of marked weakness. When first examined in the hospital he appeared to be in profound shock. The radial pulse was not detectable and his blood pressure was not obtainable. Examination of the chest showed a stab wound in the fourth intercostal space, 5 cm. to the left of the sternum. The heart sounds were distant and muffled and the cervical veins were full. These signs were thought to indicate hemopericardium with cardiac tamponade. An operation was deemed urgent and was performed under local infiltration

* A detailed report of the surgical aspects of these cases will appear in the Proceedings of the Southern Medical Association for 1931.

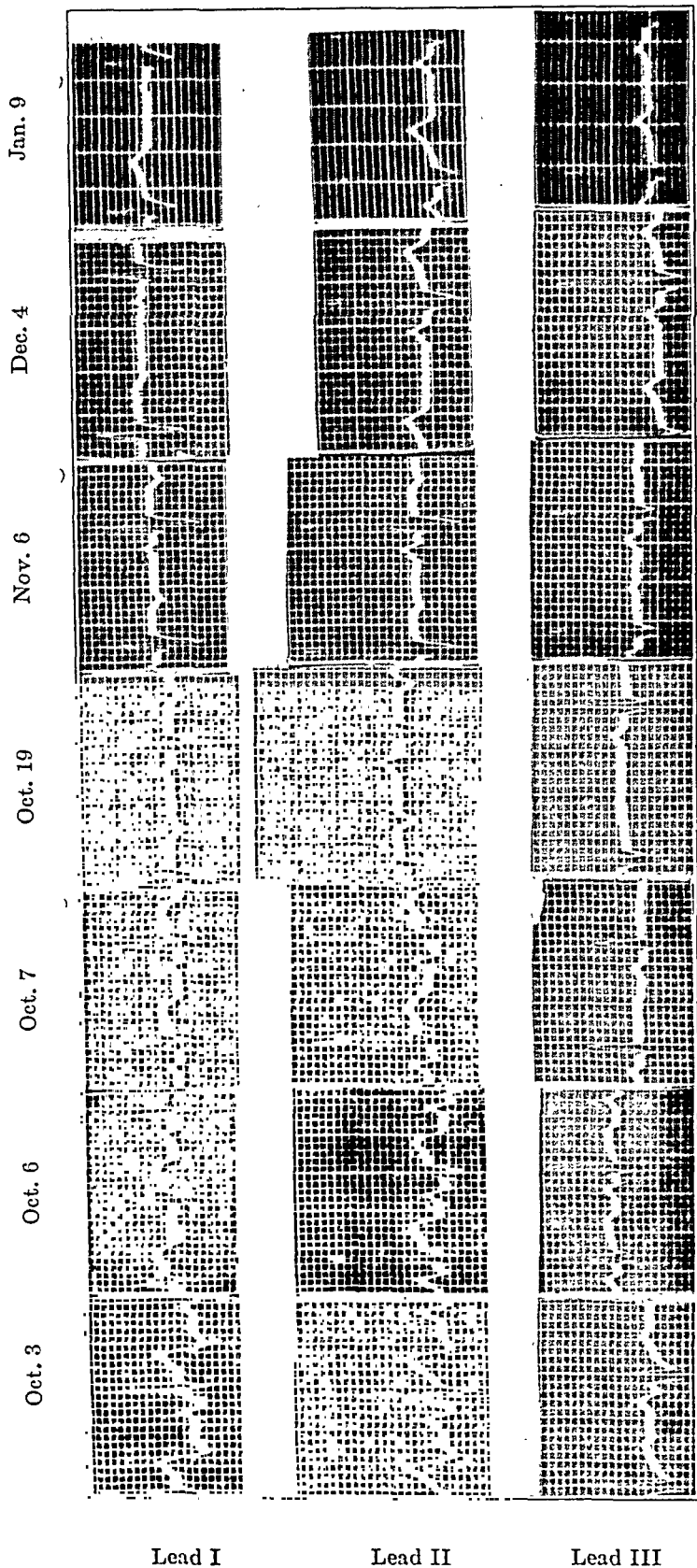


CHART I.—Case 1. The first electrocardiogram was made 14 hours after the operative repair of the wound. The changes noted are characteristic of those seen in coronary thrombosis. The electrocardiogram of January 9 shows a complete return to normal.

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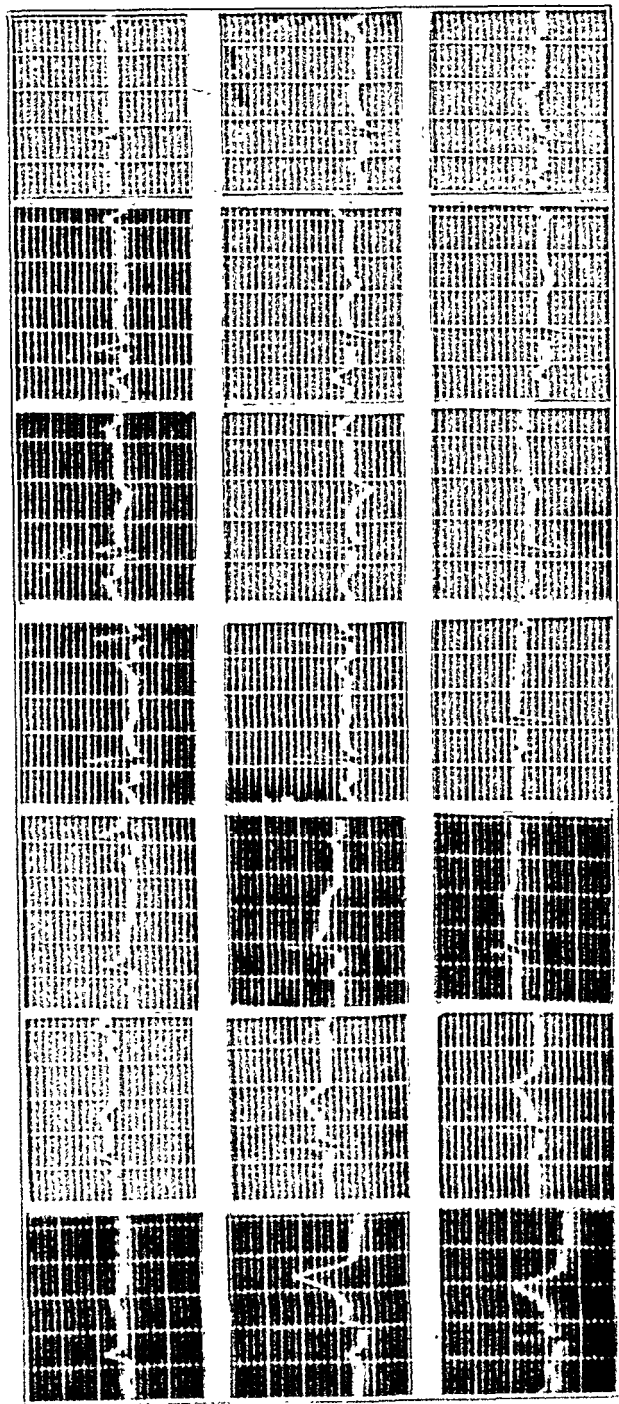
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July 6

July 5



Lead I

Lead II

Lead III

CHART II.—Case 2. The first electrocardiogram was made 9 hours after the operative repair of the wound. The changes noted are characteristic of those observed in coronary thrombosis involving this area of the heart muscle.

anesthesia. When the pericardium was incised more than 200 cc. of blood were evacuated and bright red blood was found to be spurting from a wound in the left ventricle. A wound, 1 cm. in length, was found on the left border of the heart (Fig. 1) parallel to its long axis and about 5 cm. from the apex. The descending branch of the left circumflex coronary artery had been divided. The wound was closed with three interrupted sutures and the bleeding artery ligated. Incision of the pericardial sac had produced a prompt improvement in the pulse rate and volume.

The patient was discharged in good condition 16 days after the injury. Seen in April, 1931, he stated that he was doing routinely the work of a laborer. At that time physical examination, electrocardiographic and Roentgen ray studies of the heart revealed no phenomena indicative of cardiac disease. Chart I illustrates the electrocardiograms taken while in the hospital and since his release.

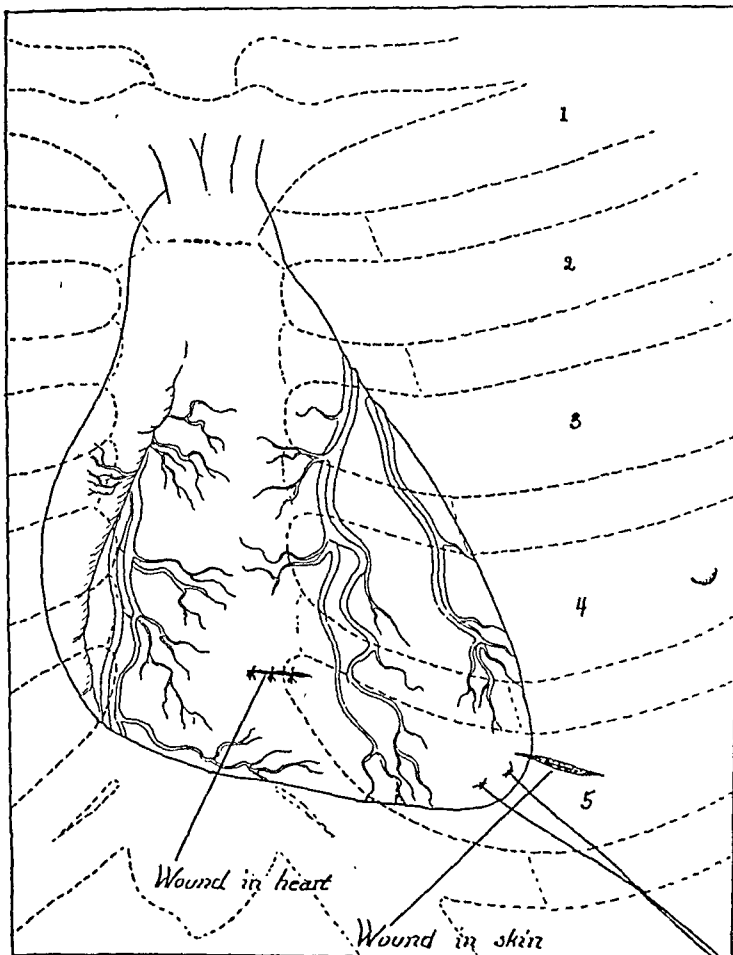


FIG. 2.—Case 2. The approximate location and size of the wound in the right ventricle.

CASE 2.—W. J., negro, male, aged 36 years, entered St. Philip Hospital at 11 P.M., July 4, 1931. He stated that he had been stabbed in the chest with a pocket knife about 7 P.M., after which he ran about 50 yards and fell to the ground unconscious. He was put in a car and carried 5 miles to a physician who noted that the patient was bleeding freely from the chest

wound and was in profound shock. He was given morphin and atropin and placed on a table with his feet elevated. In about 15 minutes the pulse became palpable and the skin warm. The patient was brought 20 miles to the hospital and when admitted his systolic blood pressure was 112 mm. Hg. and pulse rate 90 per minute. A stab wound was noted 5 cm. from the midsternal line in the fifth intercostal space. The area of cardiac dullness was not definitely increased, but the heart sounds were distant and muffled. A diagnosis of stab wound of the heart was made from the history with suggestion of a cardiac tamponade, which had probably been relieved by the free bleeding from the chest wound. The operation was performed under local infiltration anesthesia. Only a moderate amount of blood was found in the pericardial sac, but there was a constant flow of dark blood from a transverse wound 1.5 cm. in length in the mid-portion of the anterior wall of the right ventricle, about 5 cm. above the apex level. (Fig. 2.) The wound was closed with three interrupted sutures of fine silk. The patient's course in the hospital was uneventful, except for a mild local staphylococcic wound infection. The patient has been followed since leaving the hospital and was studied completely 7 months after the accident, all studies failing to reveal any pathologic aftermath. Chart II illustrates the electrocardiographic changes noted while in the hospital and 2 months after his discharge from the surgical service.

Discussion. The lesion produced in the heart muscle in each case consisted of a puncture wound from a sharp-edged weapon which divided cardiac muscle fibers and in Case 1 sectioned a branch of the left coronary artery. The end result following surgical repair was an area, 1 to 2 cm. in diameter, with the muscle fibers enmeshed in suture material and drawn sufficiently tight to control bleeding, and in Case 1 the injured coronary vessel was ligated. It is reasonable to assume that local ischemia existed at the point of the repaired wound, and in Case 1 in the area supplied by the artery which was tied. In each instance collateral circulation might conceivably overcome the induced ischemia, but this would require several hours and probably a much longer period.

The electrocardiograms made following the operations are similar in every respect to those noted in coronary occlusion, and probably have the same pathologic significance. The only other logical explanation for significant changes in the electrocardiograms would be the effect of an accumulation of fluid in the pericardial sac. This factor was excluded by Roentgen ray studies at frequent intervals. For the first few days following the operation these studies were made daily. Fluid did accumulate in Case 1 to the extent of embarrassing the venous return to the heart eighteen hours after operation. It is interesting to note that changes previously observed in the electrocardiograms remained constant after the fluid was evacuated by opening the wound, yet all phenomena of cardiac tamponade were promptly relieved.

The infrequent association of cardiac pain with wounds of the heart muscle is of peculiar significance. In the 2 cases here presented pain of anginal type was entirely absent at any period before, during or after operative repair, and the operation was done with

the use of a local anesthetic injected only in the chest wall. Neither patient was sufficiently ill at the time of the operation or afterward to modify his perception or consciousness of pain. It may be profitable, therefore, to consider the significance of the absence of pain in heart muscle wounds, especially those involving the coronary vessels as related to the pathogenesis of cardiac pain in angina pectoris.

Keefer and Resnick¹ have recently reviewed completely the accumulated evidence dealing with the various factors concerned in the pathogenesis of angina pectoris. They contend that the most tenable hypothesis is that this syndrome is related directly to conditions which induce ischemia of the heart muscle, and that the pain of coronary thrombosis is of the same fundamental nature. They comment upon the interesting clinical fact that the pain of myocardial infarction tends to subside with the development of heart muscle degeneration and eventually disappears entirely. Sutton and Lueth² have recently presented experimental evidence, which they feel proves conclusively that myocardial ischemia is fundamental in the production of cardiac pain.

The studies of MacWilliam and Webster³ on the sensory phenomena associated with defective blood supply to the working muscle indicates that the pain of ischemia occurs only when the muscle is exercised under conditions inducing inadequate oxygen supply.

Lewis and his coworkers⁴ in their studies in intermittent claudication have shown that the pain in this syndrome is due to a substance generated during muscle contraction which accumulated to a concentration sufficient to induce pain and remains stable in the tissue spaces during circulatory arrest.

Angina pectoris occurs in those patients in whom contractile power of the heart muscle is better preserved and frequently disappears when congestive heart failure supervenes. This would indicate that the pain is caused by a substance dependent upon muscle contraction under special conditions, for those factors which induce pain do so by increasing heart muscle work. If one transfers the recent observations made on the mechanism of pain in skeletal muscle to the wounds of heart muscle here studied, one finds a reasonable explanation for the absence of pain, although heart muscle ischemia existed.

The wound in either of the cases presented consisted primarily of a severance of the muscle fibers extending in depth the entire thickness of the heart wall. The area of ischemia resulting from repair of the wound, which in one involved the placing of a ligature on a coronary artery, embraced an area of heart muscle which had been so injured by the penetrating weapon that normal contraction could not occur. The pain producing metabolites which form during muscle contraction and accumulate in the tissue spaces to a concentration sufficient to induce pain were therefore not produced,

though absolute or relative circulatory arrest existed. That the absence of pain was due to a rapid relief of ischemia by collateral circulation is not tenable. The nature of the lesion and subsequent changes in the electrocardiogram indicate that an injury to the heart muscle similar in nature to that occurring in coronary thrombosis was induced by the wound and operative repair.

If the absence of pain in patients with penetrating wounds of the heart muscle, who have as a result of the wound and operative repair an area of myocardial ischemia, is here given the correct explanation, it logically follows that certain aspects of angina pectoris are accounted for. The angina pectoris of effort is relieved by cessation of exercise, for the degree of myocardial ischemia is insufficient to allow the pain producing substance to remain in the tissue spaces in sufficient concentration, under the conditions of reduced rate of formation consequent upon body rest. The pain of coronary occlusion with acute ischemia in the infarcted area of heart muscle gradually lessens with the development of muscle degeneration and finally ceases when this has developed to a degree incompatible with muscular contraction.

These observations emphasize the importance of myocardial ischemia as a fundamental factor in the mechanism of angina pectoris, but at the same time suggest that heart pain will not occur if the ischemic area involves muscle tissue degenerated sufficiently to impair its contractile power.

A case reported by Burian⁵ of a wound of the heart which severed a branch of the left coronary artery, but involved only superficial layers of the heart muscle, has a direct bearing on the cases under consideration. His patient following the repair of the wound, which consisted mainly in tying the bleeding vessel, had postoperative anginal pain which he stated was a troublesome symptom. The anginal attacks were attributed by him to an area of heart-muscle anemia. In the light of recent data and the cases here studied it would appear logical to assume that the origin of pain was due to the contraction of heart muscle under ischemic conditions, the superficial nature of the lesion not interfering with this function in the area supplied by the severed vessel. This case is contradictory to the observations of Sutton and Lueth², for they noted that pain was not produced in dogs if the continuity of the vessel or the adventitia was broken.

REFERENCES.

1. Keefer, C. S., and Resnick, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, *Arch. Int. Med.*, 1928, **41**, 769.
2. Sutton, D. C., and Lueth, H. C.: Pain: Experimental Production of Pain on Excitation of the Heart and Great Vessels, *Arch. Int. Med.*, 1930, **45**, 6.
3. MacWilliam, J. A., and Webster, W. J.: Some Applications of Physiology to Medicine: I. Sensory Phenomena Associated With Defective Blood Supply to Working Muscles, *Brit. Med. J.*, 1923, **1**, 51.
4. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, *Heart*, 1920-1931, **15**, 359.
5. Burian, F.: Operation in Two Cases of Cardiac Wounds, *Casof. Lel. Cesk.*, 1922, **61**, 585.

THE USE OF BACTERIOPHAGES IN WOUND INFECTIONS AND IN BACTEREMIAS.*

BY WARD J. MACNEAL, M.D.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, NEW YORK POST-GRADUATE
MEDICAL SCHOOL AND HOSPITAL, NEW YORK CITY.

DURING a study of filterable viruses in 1915 Twort¹ observed in his cultures of smallpox vaccine a curious progressive dissolution of bacterial colonies. By transfer of material from the location on the plate, where a colony had dissolved, to the edge of a normal bacterial colony, he was able to initiate the lytic process in the latter situation and to continue such transmission from colony to colony in series. Twort regarded the phenomenon as a transmissible disease of bacteria, most probably caused by a filterable virus. Subsequent writers have contributed an abundant discussion in regard to the nature of bacteriophage, without adding materially to the original conception of Twort. d'Herelle² subsequently observed a similar phenomenon in cultures of the Shiga bacillus, particularly when derived from the intestinal contents of patients recovering from bacillary dysentery. He was able to transmit the filterable agent from culture to culture and to use it with success in the treatment of dysentery by administering it to the patients. Subsequent investigators have been able to recognize a large number of these filterable agents which are capable of bringing about the destruction of different kinds of bacteria. Of particular interest is the bacteriophage active against the staphylococcus which has been studied by Gratia.³ The results of recent investigations offer some hope that it may be possible to find agents of this sort which are effective against many of the various bacterial causes of disease.

The Nature of Bacteriophage. The question as to the nature of bacteriophage cannot be adequately answered at present. We are not in a position to say exactly what filterable viruses are, although most bacteriologists are inclined to regard them as living beings. The bacteriophage certainly shows many characteristics which are similar to those of filterable viruses and many are inclined to agree with Twort that the bacteriophage should be classed as a filterable virus. This view, however, is disputed by some, who are inclined to regard the bacteriophage as some sort of an enzyme which is liberated upon the disintegration of the bacteria.

Combat of Infections With Bacteriophage. The use of bacteriophage in the treatment of infectious diseases was suggested by Twort, but

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he found no opportunity to undertake such a study. d'Herelle has been the chief exponent of such practical use. In general, one must recognize that the problem presents a somewhat different aspect, depending upon the location of the infectious process. When the infecting microbes are growing upon epithelial surfaces or in the tissues very close to the surface the application of the bacteriophage can be made directly. In such a disease as bacillary dysentery the microorganisms ordinarily penetrate only a short distance into the tissues and the bacteriophage may be introduced into the intestinal lumen and thus reach the bacteria. Infections of the urinary tract with colon bacilli present a somewhat similar relationship. Although these bacteria may sometimes penetrate deeply into the substance of the kidney or even reach the blood stream, they tend in most instances to remain on the epithelial surface or in the immediately adjacent tissues. Infections of the nasal mucous membrane and the nasal sinuses behave in a similar way. In applying the bacteriophage to disease of this sort one is ordinarily able to reach the bacteria without introducing the bacteriophage into the blood stream or the lymph spaces.

When one approaches the treatment of infections more deeply situated in the tissues of the body, the problem is complicated by the necessity of applying the bacteriophage in the presence of the living tissues by passage through the lymph or the blood. One might assume that the bacteriophage would exhibit its characteristic effect upon the bacteria in such a situation just as it does upon the agar plate or in the broth culture in the test tube. Such, however, is not the case. Numerous studies, some of which have been carried out in our own laboratory, clearly indicate that the combat between the bacteriophage and the bacteria is profoundly influenced by the presence of various environmental factors. In particular we may mention such things as the presence of blood,⁴ of blood serum and of purulent exudate, the chemical reaction of the media,⁵ the presence of various antiseptics and the temperature. In the combat against these internal infections the presence of purulent exudate and of blood can hardly be avoided. One can hardly expect, therefore, that the bacteriophage will destroy the bacteria in a dramatic fashion when the combat takes place in the interior of the body. In fact our experience in this field has persuaded us that the bacteriophage has a much less marked effect in such cases and that it may succeed merely because it produces a slight alteration in the bacterial bodies so that they are rendered more susceptible to the ordinary defensive mechanisms of the body, such as the phagocytic leukocytes. It is evident that much more detailed studies will be required before we fully understand the events which take place in an inflammatory lesion under treatment with bacteriophage in the interior of the body.

Clinical Applications. The principal interest of this audience doubtless concerns the application of bacteriophage in the treatment of particular clinical entities, and I have chosen to speak more especially of our experience with infected surgical wounds and bacteremias. The application of bacteriophage to the treatment of furuncles and carbuncles⁶ seems to be on well-established basis. We advise that the staphylococcus bacteriophage be introduced into the lymph spaces about the boil through a very fine needle, and that this injection treatment by multiple punctures be repeated after about 48 hours. A considerable experience with furuncles and carbuncles has led my associates and me to the opinion that lesions of this sort due to staphylococcus should be treated with bacteriophage routinely. We recognize, however, that boils get well when treated in various ways and, on this account, any new method of treatment may not rapidly replace other procedures. It does seem, however, that the surgical excision of carbuncles might well be delayed until bacteriophage has been given a trial.

Infected wounds, whether accidental or surgical, have been treated by bacteriophage in several instances with good success. When the infection is chiefly by *Staphylococcus aureus*, local applications of dressings wet with the staphylococcus broth bacteriophage filtrate usually bring about rapid improvement. The purulent exudate is washed away, healthy granulations appear and the wound proceeds to prompt healing.

A more difficult situation is presented by those wounds which are continually reinfected by intestinal contents. We have had to deal with instances of this sort in which an operative incision in the abdominal wall has become soiled with intestinal contents by perforation of the intestine, recognized some time after the surgical operation. Such fistulous tracts have been treated by application of large amounts of mixed bacteriophage preparations, including bacteriophages active against staphylococcus, colon bacillus, dysentery bacilli and *Bacillus pyocyaneus*. In 2 instances the patients have done very well and the surgeons have expressed themselves as surprised at the success of the treatment.

Bacterial infections of the blood stream⁷ present a much more serious problem. In these one is practically always dealing with a pure culture of bacteria. We have had most experience with infections of this type due to the staphylococcus. When blood stream infection is a sequel of a local staphylococcus wound infection we recommend application of large quantities of the bacteriophage to the surface of the wound. At the same time, however, the intravenous injection of the bacteriophage is undertaken. For this purpose we employ a special filtrate prepared in a culture medium without protein and containing asparagin as the important source of nitrogen. This bacteriophage preparation does not of itself produce serious toxic symptoms in animals and it seems to be far less

dangerous to the patient than is the filtrate of broth culture. Staphylococcus bacteremia is a disease with high mortality and one does not undertake its treatment without recognizing that failure will be commonly met with. We have, however, had an opportunity to observe some instances of actual recovery after repeated positive blood cultures in staphylococcus bacteremia.

As a sequel to bacteremia one meets with metastatic localizations of the inflammatory process. Here we may mention especially osteomyelitis⁸ which is so common in children, inflammation of the pericardium and localization on the endocardium. The treatment of these localizations by bacteriophage presents very serious difficulties, which we have so far not been able to overcome and at present it seems that here surgical drainage when applicable will, as a rule, be required in order to offer any hopeful outlook for bacteriophage therapy.

Specificity of Bacteriophage. Some physicians think that the bacteriophage is a single agent and that the same bacteriophage may be employed against various infecting bacteria. This is unfortunately not a correct idea. It is true that some of these lytic agents are capable of attacking two or more related kinds of bacteria such, for example, as the Shiga bacillus and the Flexner bacillus of dysentery. Such polyvalency is, however, not the rule. One finds that the colon bacillus can grow actively in the bacteriophage broth filtrate active against staphylococcus. As a rule, therefore, an accurate etiologic diagnosis is necessary before one can apply bacteriophage therapy with hope of success. We do not insist that bacteriologic cultures are necessary before one can begin treatment. Certainly some diseases, such for example as furunculosis, can be diagnosed with considerable accuracy as to etiology, so that treatment may be begun while waiting for the cultures to develop. It is necessary to emphasize that bacteriophage is not a general antiseptic. As a matter of fact, the bacteriophage preparation is a good culture medium for bacteria other than the particular organisms against which the bacteriophage is potent.

Incompatibilities of Bacteriophage. It also seems important to emphasize the incompatibility of bacteriophage therapy. This agent should be employed under conditions which favor its action and offer it at least a reasonable opportunity to attack the bacteria. On epithelial surfaces, therefore, it is important that the chemical reaction of the medium should be suitable. The presence of chemical germicides or antiseptics seriously interferes with the action of the bacteriophage. It is also necessary to recognize that inflammatory exudates, blood serum and blood itself interfere with the efficiency of this agent. We have met with considerable difficulty in impressing the importance of these considerations upon some of our clinical associates who have been interested in combining bacteriophage therapy with other procedures.

A few records of individual patients have been selected for brief mention in order to illustrate the character of our experience.

Clinical Notes. CASE 1.—A man, seen in 1929, with repeated positive blood cultures, staphylococcus abundant in urine and in sputum, was given bacteriophage subcutaneously and into the nephrectomy wound after removal of a large abscessed kidney. The pneumonia cleared and the infectious process in the second kidney gradually subsided. After a prolonged convalescence the patient returned to work and continues well.

CASE 2.—A physician developed sepsis early in 1930 after surgical removal of ureteral calculus. Blood culture repeatedly showed staphylococci in small numbers. Bacteriophage was poured into the wound. Subsequently the blood culture became negative for staphylococcus. After a prolonged convalescence, complicated by vertebral osteomyelitis, the patient has returned to the active practice of surgery.

CASE 3.—A boy, aged 15 years, with positive staphylococcus blood culture, temperature 104° to 105° F., and symptoms of early osteomyelitis and pericarditis, was given large intravenous doses of the asparagin bacteriophage; 40 cc. on January 31, 1931, and 74 cc. on February 2, 1931; a total of over 900 cc. during the course of the illness, which terminated in death on February 24. Blood cultures taken after February 2 remained negative, but the pericardial exudate contained living staphylococci at the end.

CASE 4.—A boy, aged 12 years, with about 50 staphylococci per cc. of blood, was operated upon for acute osteomyelitis of right femur and right tibia. During the following 6 days he received the equivalent of 80.3 cc. of undiluted asparagin bacteriophage in divided doses. Blood culture taken shortly before death from massive pneumonia, on the sixth day, was still positive for staphylococcus.

CASE 5.—A physician, aged 24 years, with a furuncle on upper lip and cellulitis of face, temperature 104.6° F., had a negative blood culture taken, December 6, 1931, at 9 P.M. Immediately thereafter bacteriophage was injected intravenously. Temporary improvement was followed by extension of the process. Blood culture, taken December 8, 1931, showed about 170 colonies of staphylococcus per cc. of blood. Local injections of bacteriophage into the facial tissues were given on December 8. The patient died, December 11.

CASE 6.—A young woman showed *Bacillus coli* in blood culture following septic abortion, with temperature up to 106° F. The pelvic condition was considered inoperable. Intravenous bacteriophage injections produced frightful reactions. The blood culture became negative in 3 days and the patient recovered completely after several weeks in hospital.

CASE 7.—A woman, aged 34 years, developed fecal fistula after removal of an inflamed papillary cyst from the pelvis. Irrigation of the sinus with a mixture of various bacteriophage preparations was followed by amelioration of symptoms and slow convalescence. The patient has returned to work.

The very brief recital of these cases may be misleading and may cause you to think that bacteriophage therapy is a dramatic, sudden and decisive remedy for severe infections. I prefer rather to regard it as a helping hand, which sometimes seems able to tip the balance in favor of recovery of the patient. Greater clinical experience may make possible a more intelligent use of these agents with, possibly, an improvement in results.

REFERENCES.

1. Twort, F. W.: An Investigation on the Nature of Ultramicroscopic Viruses, *Lancet*, 1915, 2, 1241.
2. d'Herelle, F.: *The Bacteriophage and Its Behavior*, translated by George H. Smith, Baltimore, Williams & Wilkins Company, 1926, pp. xiv + 629; *Bacteriophage as a Treatment in Acute Medical and Surgical Infections*, *Bull. New York Acad. Med.*, 1931, 7, 329.
3. Gratia, André: Le traitement des infections à staphylocoques par le bactériophage et les mycolysats staphylococciques, *Bull. et mém. Soc. nat. de chir.*, March 5, 1930.
4. Applebaum, M., and MacNeal, W. J.: The Influence of Pus and Blood upon the Action of Bacteriophage, *Proc. New York Path. Soc., Arch. Path.*, 1931, 11, 680; *J. Inf. Dis.*, 1931, 49, 225.
5. Frisbee, F. C., and MacNeal, W. J.: The Behavior of *Escherichia coli* and Its Specific Bacteriophage in Urine, *Proc. New York Path. Soc., Arch. Path.*, 1930, 9, 1116; *J. Inf. Dis.*, 1930, 46, 405.
6. Cipollaro, A. C., and Sheplar, A. E.: Therapeutic Uses of Bacteriophage in the Pyodermata, presented at Annual Meeting of the American Medical Association, Philadelphia, June 11, 1931, *Arch. Dermat. and Syph.*, 1932, 25, 280.
7. MacNeal, W. J.: Bacteriophages as a Help in the Treatment of Infections in Children, *New York State J. Med.*, 1931, 31, 1383.
8. Patterson, M. B., and Albee, F. H.: Bacteriophage in Relation to Healing of Osteomyelitis, *Proc. Soc. Exp. Biol. and Med.*, 1930, 27, 376.

OBSERVATIONS ON THE EFFECTS OF OXYGEN THERAPY. II. CHANGES IN THE CIRCULATION AND RESPIRATION.*

By LOUIS N. KATZ, M.D.,

PHYSIOLOGIST AND DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE HOSPITAL; ASSISTANT PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF CHICAGO,

WALTER W. HAMBURGER, M.D.,

ATTENDING PHYSICIAN, MICHAEL REESE HOSPITAL; ASSISTANT CLINICAL PROFESSOR OF MEDICINE, RUSH MEDICAL COLLEGE, UNIVERSITY OF CHICAGO,

AND

SAMUEL H. RUBINFELD, M.D.,

PHYSIOLOGY INTERNE, MICHAEL REESE HOSPITAL,
CHICAGO, ILL.

(From the Heart Station, Michael Reese Hospital.)

MEASUREMENTS of the circulation and respiration, similar to those already reported in the literature and summarized in our first report,¹ were made as part of the study of the effects of oxygen therapy. These determinations were undertaken to serve not only as a quantitative check of the clinical observations but also to attempt to determine whether they were simply a measure of the clinical condition and varied with the clinical course or, on the other hand, whether they were dependent on the use of the oxygen-rich atmosphere and were therefore in part responsible for the clinical changes noted.

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In order to evaluate these alternatives, observations were made, not only on 6 cardiac patients, but also on subjects who might serve as controls—2 patients with pneumonia, 4 with hyperthyroidism, 1 young diabetic, and 2 healthy individuals. The “noncardiac cases” served, in a way, as a control. As far as possible the observations during oxygen treatment were controlled in each case by determinations during a period before and after the oxygen treatment. The management of the patients was first stabilized and remained unaltered unless the condition became progressively worse during oxygen treatment. The measurements included in the present report will deal with (1) vital capacity, (2) breath-holding, (3) minute volume of respiration, (4) heart rate, (5) arterial blood pressure, (6) venous blood pressure, and (7) the electrocardiogram.

Measurement of Respiration. The minute volume of respiration was determined by measuring the volume of expired air collected in a small spirometer (Sanborn vital capacity model). A two-way flap valve was used to direct the expired air into the spirometer. A three-way stopcock in the line was employed to connect and disconnect the patient with this spirometer. The connections were made and broken at the beginning of an inspiration, the time of collection being noted with a stopwatch; from these data the minute volume of respiration was then calculated. The vital capacity was measured in the usual way. The “breath-holding” time was determined after a normal inspiration, the patient being instructed to stop breathing as long as possible.

In Table 1 are assembled the data of the more completely studied cases. It was not always possible to get complete data, because of the clinical condition, especially in the cardiac patients. The minute volume of respiration in the cardiac patients paralleled the clinical course. The decreased breathing did not precede the other evidence of improvement when improvement occurred. It is interesting to note that in 3 of the 4 hyperthyroid patients and in both of the normal patients a decrease in minute volume of breathing was noted in the oxygen atmosphere; this was associated with a decrease in depth rather than with a diminution in rate. Furthermore, these alterations were associated with only slight changes in arterial oxygen saturation and in one of the normal cases (LK) with no change at all (*cf.* our other report²). Apparently some other mechanism besides relief of arterial anoxemia is at least partly responsible for the decrease in breathing. The possibilities exist that the oxygen-rich environment alters the blood in some way, *viz.*, by a tendency toward an alkaline pH, and so depresses the respiratory center, or that the stay in a high oxygen environment sets up reflexes from the alveoli to depress breathing. The increase in CO₂ content of the arterial blood (*cf.* our other report²) may be in part due to the decrease in breathing. The improvement in breathing is appar-

TABLE 1.—ANALYSIS OF DATA.

Patient and condition.	Breath-holding, sec.	Vital capacity, liters.	Minute volume of breathing, liters per min.	Arterial blood pressure, mm. Hg.	Venous pressure.	
					Direct, mm.H ₂ O.	Indirect, mm.H ₂ O.
LK—Normal						
Before O ₂ . .	59	3.5	10.0	108/58	15	40
During O ₂ . .	51	3.4	6.8	108/70	70	10
After O ₂ . .	43	3.4	8.0	112/72	35	110
SS—Normal						
Before O ₂ . .	84	3.6	5.7	102/70	150	90
During O ₂ . .	113	3.8	5.6	100/70	110	110
After O ₂ . .	76	3.7	4.5	98/68	90	..
PI—Thyroid						
Before O ₂ . .	7	1.9	6.1	146/70	100	110
During O ₂ . .	11	1.6	4.4	140/86	55	..
After O ₂ . .	7.5	2.0	5.3	160/90	..	95
RA—Thyroid						
Before O ₂ . .	23	1.3	9.8	210/110	..	70
During O ₂ . .	45	0.9	7.6	208/116	20	..
After O ₂ . .	21.5	1.3	9.0	198/104	60	100
SCH—Thyroid						
Before O ₂ . .	33	2.9	5.4	108/70	80	100
During O ₂ . .	19	2.7	3.4	110/72	..	60
After O ₂ . .	19	2.5	6.0	108/66	40	40
CO—Thyroid						
Before O ₂ . .	15	1.9	..	128/70	75	80
During O ₂ . .	22	1.5	7.2	110/68	..	60
After O ₂ . .	14	1.6	7.5	126/64	75	80
BR—Cardiac						
Before O ₂ . .	17	2.3	27.7	117/74	90	95
During O ₂ . .	35	1.8	8.1	140/86	10	25
During O ₂ . .	17	1.5	11.4	132/88	150	..
After O ₂ . .	24	2.1	17.9	158/80	30	50
BER—Cardiac						
Before O ₂ . .	13	1.4	3.9	150/92	150	..
During O ₂ . .	20	1.1	3.1	130/90	..	60
Out of O ₂ . .	24	1.1	4.7	118/90	140	150
During O ₂ . .	12	1.1	3.2	170/92	125	90
After O ₂ . .	17	1.3	8.0	140/80
GE—Cardiac						
Before O ₂ . .	21	120/80
During O ₂ . .	25	120/80
During O ₂ . .	33	110/74
After O ₂ . .						
BA—Cardiac						
Before O ₂ . .	5	1.0	8.0	140/80	70	..
During O ₂ . .	6	0.8	8.0	140/96	35	50
After O ₂ . .	4	0.6	..	160/90

ently easily masked when the clinical course of the patient is progressively downgrade in oxygen; for example, one case (BA) while in oxygen showed no improvement in breathing due apparently to the associated progression of the decompensation.

The slowing in breathing was not accompanied by an increase in vital capacity in the cases in which the latter was measured, but in most cases by a slight but definite decrease in vital capacity (Table 1). This occurred also in the 3 cardiac cases in whom a complete set of observations of vital capacity were made. The decrease in minute volume cannot therefore be ascribed to an alteration in vital capacity, since it occurred when the vital capacity was unchanged or actually decreased slightly.

The length of time the breath was held was increased in practically all the "noncardiac cases" in which this item was studied and also in most of the cardiac cases, sometimes even when the patient became clinically worse. The test, however, is not entirely satisfactory in patients because the psychic element is a variable which seems to be a large factor in determining the time of breath-holding. Furthermore, the breath should be held longer in oxygen since the alveolar oxygen content is higher than in ordinary atmospheres and the stimulating effect of asphyxia on breathing therefore would be delayed. This extra store of oxygen in the alveoli while in an oxygen-rich environment may be of importance in preventing or minimizing an unsaturation of arterial blood which might otherwise ensue during quick adjustment to extra demands of the body tissues for oxygen.

Measurements of Circulation. The ordinary auscultatory method was used for estimating arterial blood pressure. Venous pressure was measured by Eyster's³ indirect method and by a direct method modified from Moritz and Tabora.⁴ The latter consists of an adjustable 1-cc. pipette, (*Pp*) Fig. 1, mounted on a millimeter rule (*S*) and connected by a T-tube (*TT*) to a needle adaptor (*A*) and a 21-gauge needle to be inserted into the vein. The other connection of the T-tube is to a small separatory funnel (*SF*); small stopcocks (*SC*) having been placed in the rubber tubing leading from the T-tube to the needle and in the tubing leading to the reservoir, so that the pipette can be separated from the reservoir and connected to the needle in the vein or *vice versa*. The apparatus is sterilized before using and filled with sterile physiologic saline solution. The pipette is made movable on the mm. ruler so that it can be shifted until the level of fluid is stationary. In this way, movement of blood into the needle and movement of saline into the vein are minimized. As a check, to assure the patency of the needle, the pipette is shifted slightly to see if the fluid returns to its original level. The level on the scale is read and corrected for the zero level of the right auricle. Tests showed that the indirect method did not always check with the direct, differing by as much as 60 mm.

of H_2O (Table 1). For these reasons it seems to us the direct method is more satisfactory than the ordinary indirect method and no more complicated. It deserves to be used more than it has been in the past.

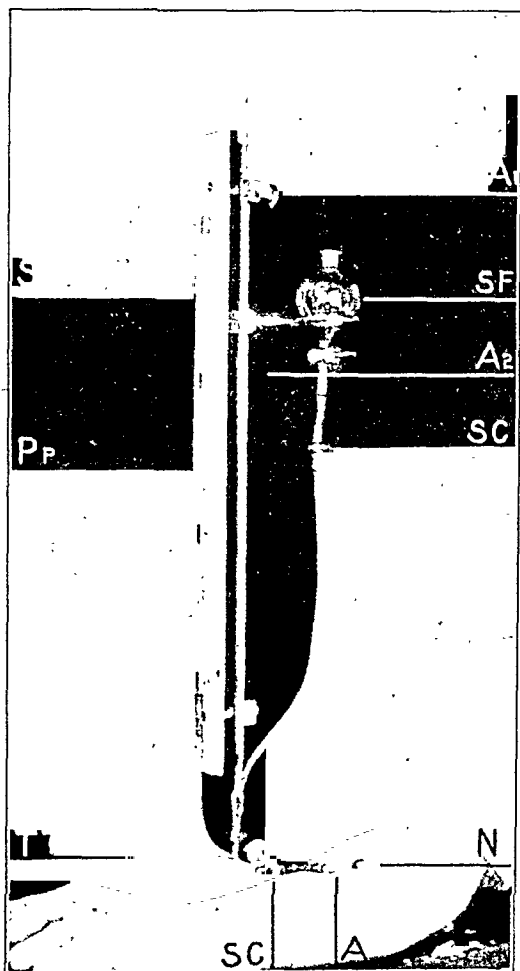


FIG. 1.—Apparatus for direct venous pressure determinations. *S*, millimeter rule with clips for pipette; *Pp*, 1-cc. pipette; *TT*, T-tube; *SC*, stopcock; *A*, adaptor; *N*, needle; *A2*, rod of stand, *SF*, separatory funnel; *A1*, clamp holding rule on stand

The changes in heart rate were measured by one of us in the ordinary way and checked by the electrocardiogram. The water intake and output were charted in all these patients.

No significant changes in arterial blood pressure were observed in these cases while in the oxygen-rich environment (Table 1). Nor were the changes in venous pressure significantly correlated with oxygen treatment, the changes being within the range of variation

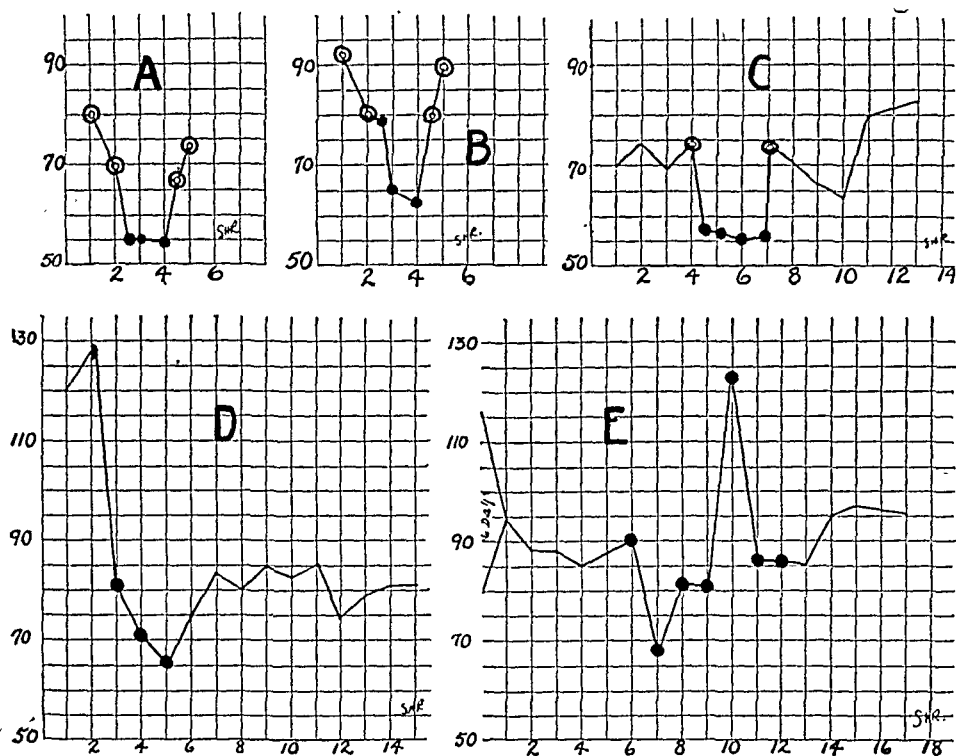


FIG. 2.—Pulse rate curve. A, B and C, controls; D, pneumonia; E, hyperthyroidism. ○, in oxygen room with normal oxygen content; ●, in oxygen-rich atmosphere; other points in ordinary air, outside oxygen room; ordinates, pulse rate per minute; abscissæ, days.

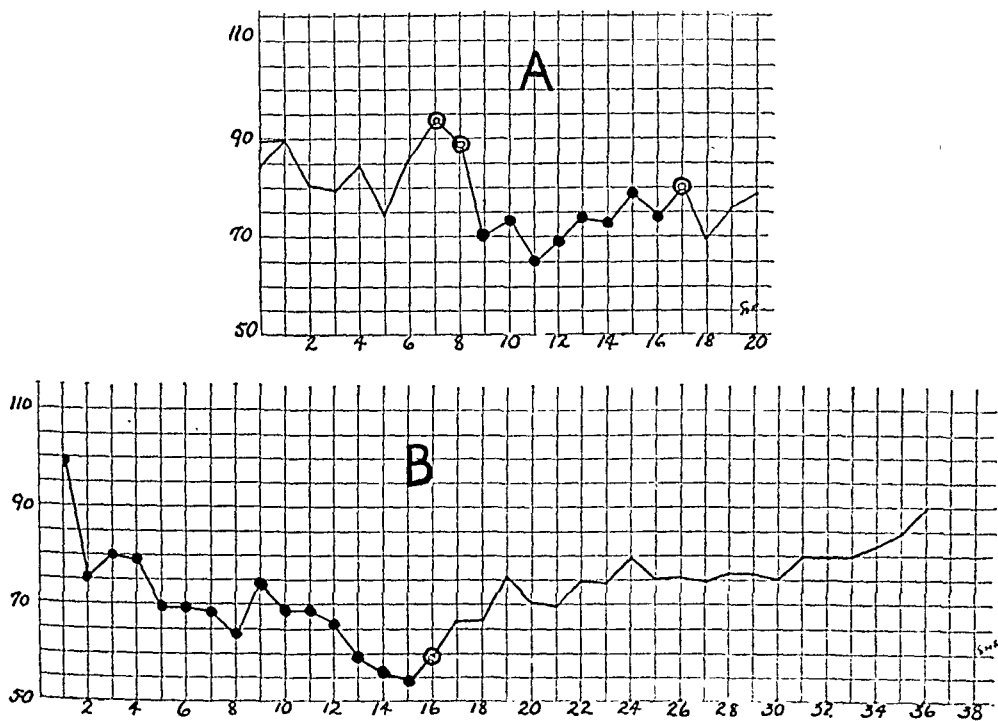


FIG. 3.—Similar to Fig. 2. A, hyperthyroidism; B, arteriosclerotic heart, recent coronary occlusion and heart failure.

to be encountered in such observations. In 1 cardiac patient (BR) the venous pressure dropped, and while in the oxygen chamber later rose again temporarily.

A striking slowing of heart rate was noted in the "noncardiac cases" during oxygen therapy (Figs. 2 *A, B, C, D, and E* and 3 *A*). A similar slowing was noted in 1 of the cardiac patients (BR) (Fig. 3 *B*), but not in the cardiac patients having persistent auricular fibrillation. This slowing might be the result of an effect exerted upon the sinus node by environmental factors in the oxygen room and tent. How this change is initiated, whether by some reflex from the alveoli or by changes in the blood, is not clear. There can be no doubt that slowing the heart rate and the diminution of the minute volume of respiration are beneficial actions of oxygen therapy which in themselves, and aside from any relief of arterial anoxemia, may help to turn the downward course of the cardiac case toward improvement. In cases with fibrillating auricles it is significant that the benefit of oxygen therapy may be lessened by the absence of the slowing of the ventricles.

The changes in the electrocardiogram, aside from the slowing in sinus rate when fibrillation of the auricles was absent, were minor. In Fig. 4 are shown segments of the electrocardiogram from a patient (*RA*) with hyperthyroidism taken before (*A*), during (*B*), and after (*C*), a stay in the oxygen room. The slowing in rate during oxygen therapy is evident. In this case, as in several other of the "non-cardiac" and cardiac patients, the *T* wave became larger and longer in two or more leads during the stay in oxygen, *i. e.*, 9 out of 13 cases studied. The increase in this particular case was confined to Leads I and II while in Lead III the *T* wave became smaller. The amplitude of *QRS* increased in all three leads in this case during oxygen administration, as occurred in 10 of the 13 cases so studied. In Fig. 5, curves obtained on a normal subject (*SS*), is shown the increase in *QRS* amplitude especially in Leads I and III, during oxygen administration. This is one of the exceptional cases which showed a decrease in the *T* wave during oxygen administration. The record does not show the slowing in pulse rate during oxygen so clearly as the chart of Fig. 2 *A* because of the marked sinus arrhythmia present in this person.

An interesting series of electrocardiograms is shown in Fig. 6 from a case of cardiac failure (BR) due to a coronary occlusion. The first record (*A*), taken on the second day in the oxygen room shows a large *Q*₃ and small inverted cove *T*₃ as the only evidence suggestive of coronary occlusion. The second record (*B*), shows the paroxysmal auricular fibrillation which was associated with an apparent second coronary occlusion which developed during his stay in the oxygen room. The following two records obtained later during the stay in oxygen show low "voltage," probably resulting from the second coronary attack. The striking slowing of the heart

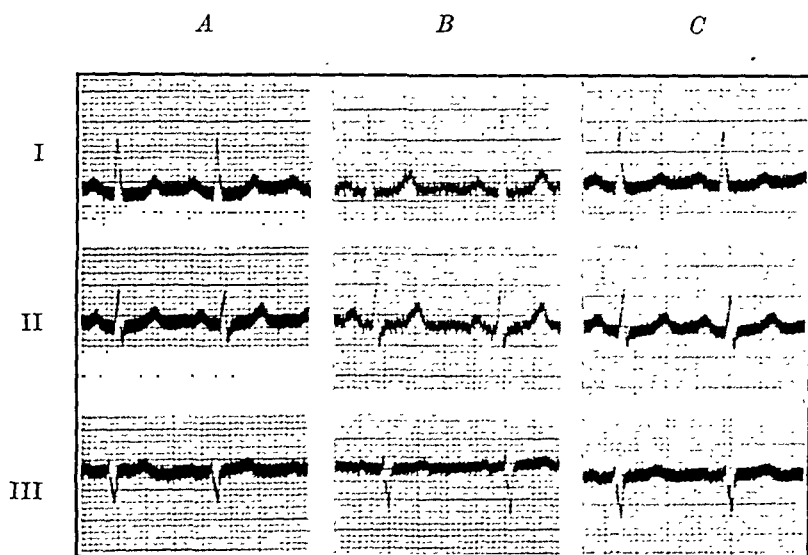


FIG. 4.—Electrocardiograms, three standard leads, on normal individual, whose pulse rate is shown in Fig. 2 A, taken before (A), during (B) and after (C) administration of oxygen.

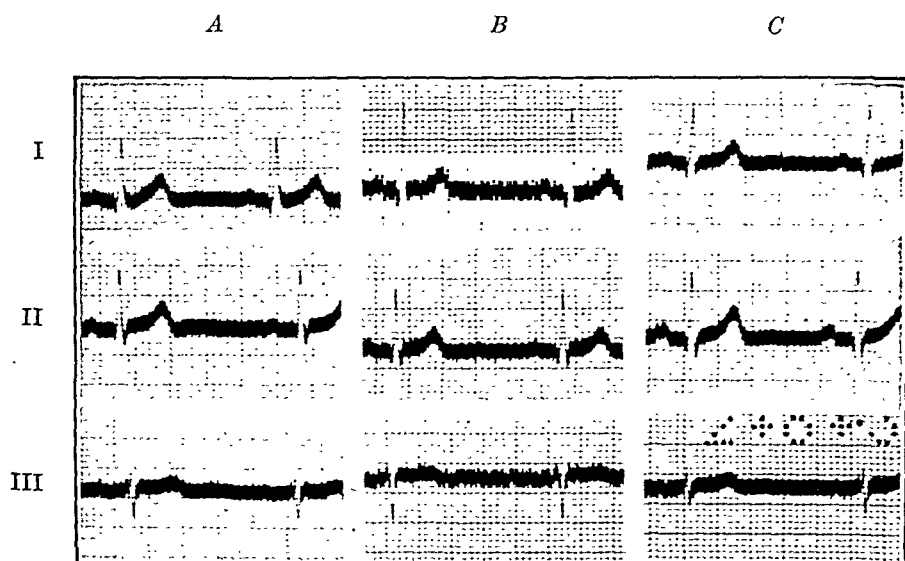


FIG. 5.—Electrocardiograms, three standard leads, on patient with hyperthyroidism, taken before (A), during (B) and after (C) administration of oxygen.

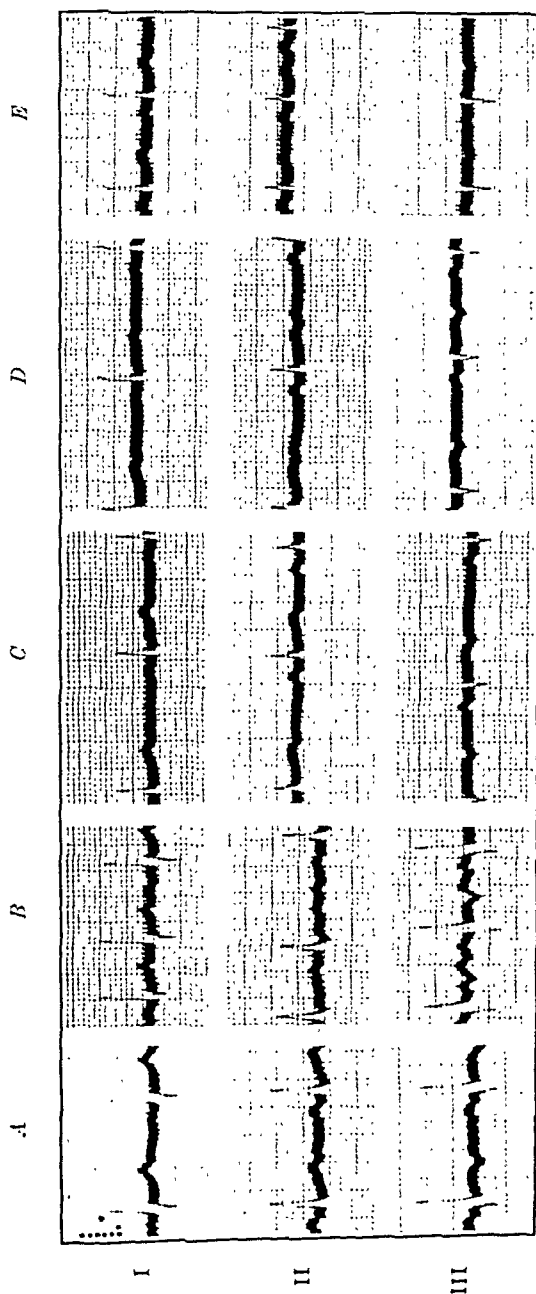


FIG. 6.—Electrocardiograms, three standard leads, on cardiac patient whose pulse rate is shown in Fig. 3 B. Curves A, B, C and D were taken during oxygen therapy, curve E after removal from oxygen room.

rate in this patient while in oxygen is seen by comparing the two records (*C* and *D*) with the last of the series shown (*E*), taken after the patient had left the oxygen chamber.

No diuretic action could be demonstrated in any of the "non-cardiac" patients while in the oxygen chamber. This was also true in those cardiac cases which did not show any striking improvement in oxygen. A decrease in edema and diuresis was, of course, found in the cardiac patients as one of the concomitants of clinical improvement, but the study of the "noncardiac" patients and normals would indicate that the diuretic action which Barach⁵ has stressed is a result of the improvement in the condition of heart and circulation and not, apparently, a direct diuretic action of the high oxygen environment. In the cardiac cases which became worse clinically during oxygen administration the edema and the oliguria increased.

Summary and Conclusions. A comparison of the effects of oxygen therapy on the circulation and respiration of a group of cardiac and "noncardiac" patients was used as a check on the clinical impressions, and to determine whether these changes preceded, accompanied or followed the clinical improvement.

A modified direct venous pressure method is described, and also a simple clinical method of determining minute volume of respiration.

Oxygen therapy tended to decrease the vital capacity slightly. It caused no significant changes in arterial and venous pressure.

An increase in the amplitude of *QRS* and an increase in the size and duration of the *T* wave was found in the majority of cases during exposure to an oxygen-rich atmosphere.

Oxygen therapy was found to result in (1) a slowing of the heart by causing a sinus bradycardia, (2) a decrease in minute-volume of respiration, and (3) an increase in the length of time the breath could be held. These changes tend to occur as readily in the "non-cardiac" case as in the cardiac, and in the latter in spite of advancing failure. These changes are primarily the result of the oxygen-rich environment and seem in part, at least, independent of relief of arterial anoxemia. These changes in heart rate, in breath-holding ability and in minute-volume of respiration are in themselves beneficial and may be ways, aside from relief of arterial anoxemia, by which oxygen therapy may act beneficially in cases of heart failure. No slowing of ventricular rate occurred in cases with auricular fibrillation, and less beneficial effects may be expected from oxygen therapy in such cases.

No direct diuretic action was observed as a result of oxygen, either in the edematous or nonedematous patients.

BIBLIOGRAPHY.

1. Hamburger, W. W., Katz, L. N., Cohn, D. J., and Rubinfeld, S. H.: Observations on the Effects of Oxygen Therapy: I. Clinical Observations, *J. Am. Med. Assn.*, 1932, 98, 1179.

2. Cohn, D. J., Katz, L. N., Soskin, S., and Hamburger, W. W.: Observations on the Effects of Oxygen Therapy: III. Blood Chemical Changes. (See next article, this number.)

3. Eyster, J. A. E.: Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929, p. 21.

4. Moritz, F., and von Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsch. Arch. f. klin. Med., 1910, 98, 475.

5. Barach, A. L., and Richards, D. W., Jr.: Effects of Treatment with Oxygen in Cardiac Failure, Arch. Int. Med., 1931, 48, 325. Barach, A. L.: The Therapeutic Use of Oxygen in Heart Disease, Ann. Int. Med., 1931, 5, 428.

OBSERVATIONS ON THE EFFECTS OF OXYGEN THERAPY.

III. BLOOD CHEMICAL CHANGES.*

By DAVID J. COHN, Ph.D.,

DIRECTOR OF CHEMICAL LABORATORIES, MICHAEL REESE HOSPITAL,

LOUIS N. KATZ, M.D.,

PHYSIOLOGIST AND DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE HOSPITAL; ASSISTANT PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF CHICAGO,

SAMUEL SOSKIN, M.D.,

DIRECTOR OF METABOLIC RESEARCH, MICHAEL REESE HOSPITAL,

AND

WALTER W. HAMBURGER, M.D.,

ATTENDING PHYSICIAN, MICHAEL REESE HOSPITAL; ASSISTANT CLINICAL PROFESSOR OF MEDICINE, RUSH MEDICAL COLLEGE, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

EXPOSURE to atmospheres containing higher percentages of oxygen than the 21 per cent present in air at sea level has been reported to be of therapeutic value in many conditions in which anoxemia is a feature; this applies particularly to conditions like pneumonia and cardiac failure in which the poor oxygenation is due mainly to decreased aëration of the blood in the lungs. These findings have been reviewed in a previous report.¹

Barach,^{3,4,5} who devised tents and rooms for the efficient administration of oxygen, has made a number of clinical and chemical studies of patients during the treatment. We have undertaken similar studies, using both oxygen tents and two oxygen rooms, and have in general confirmed the earlier work. We have, however, included normal subjects in our series, and patients with emphysema and exophthalmic goiter—conditions not hitherto reported—who also served as controls, although in a more limited way.

The clinical observations of the effects of the treatment on respiration and the circulation have been presented elsewhere.^{1,2}

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This paper is confined to the report of the chemical findings in the arterial blood of our subjects. In each case the blood was investigated for: (1) Oxygen content and capacity (the ratio of content to capacity giving the percentage oxygenation, normally about 95 per cent); (2) CO₂ content of the blood serum; (3) hydrogen ion concentration of the blood serum; (4) glucose, nonprotein nitrogen, urea, chlorids, cholesterol and lactic acid contents of whole blood.

This last group of findings showed no consistent variations that could be attributed to oxygen therapy, and are therefore omitted from the table of results (Table 1). Whenever possible, blood

TABLE 1.—BLOOD FINDINGS (ARTERIAL BLOOD).

Patient.	Date.	Per cent O ₂ saturation.			CO ₂ content.			pH.		
		Before O ₂ .	During O ₂ .	After O ₂ .	Before O ₂ .	During O ₂ .	After O ₂ .	Before O ₂ .	During O ₂ .	After O ₂ .
I. Normal S. S.	April 3 5 6	92.5		..	51.0		..	7.50		..
		..	96.0	53.0	7.45	..
		93.0	57.0	7.50
II. Normal L. K.	April 3 5 6	95.5		..	46.0		..	7.40		..
		..	95.0	50.0	7.40	..
		95.0	55.5	7.45
III. Lob. pneu. Bo.	Dec. 26 29 Mar. 19	66.5		..	51.0		..	7.35		..
		..	69.5	62.5	7.40	..
		94.0	49.0	7.55
IV. Broncho- pneu. Nim.	Dec. 31 Jan. 2 27	64.5		..	70.5	
		..	94.0	94.5	7.40	..
		91.0	62.0	7.40
V. Cardiac Ba.	Feb. 26 Mar. 5 10 17	85.0		..	41.5		..	7.55		..
		..	92.0	42.5	7.50	..
		..	83.5	64.0	7.70	..
		90.5	76.5
VI. Cardiac Ber.	Jan. 31 Feb. 5 26 Mar. 5 10 16 23	94.5		..	44.0		..	7.30		..
		42.5	7.35
		81.0		..	40.5	
		..	91.0	38.0	7.55	..
		..	85.5	45.0	7.45	..
		..	90.0	40.0	7.55
VII. Cardiac Bie.	Feb. 24 Mar. 2 9 11	..	92.0	34.5	7.50	..
		..	83.5	60.0	7.50	..
		..	92.5	57.5	7.50	..
		83.5	50.5	7.55
VIII. Emph. He.	Dec. 22 26 29 Jan. 2 Mar. 20	81.5		..	77.5		..	7.45		..
		..	88.5	91.0	7.50	..
		..	91.0	100.0	7.55	..
		81.0	85.5	7.45
		88.0	78.0	7.55
IX. Thyroid Co.	Mar. 16 18 24 31 April 1	89.0		..	48.5		..	7.40		..
		88.0		..	44.0		..	7.45		..
		..	94.0	50.5	7.45	..
		93.0	7.50
		92.5	45.0	7.50
X. Thyroid Sch.	Feb. 13 20 25 Mar. 20	87.0		7.60		..
		90.0		..	53.5		..	7.50		..
		..	96.0	61.5	7.55	..
		92.5	52.0	7.40
XI. Thyroid Rav.	Feb. 13 20 21	92.5		..	43.5		..	7.55		..
		..	97.0	64.0	7.65	..
		91.0	53.5	7.65

was drawn at least 3 times from each subject—before, during and after oxygen administration. The management of the patient, including the use of medication, was kept constant during the whole procedure unless the patient's condition was obviously growing worse despite the oxygen therapy. The condition of the patient, of course, was often an uncontrollable variable; some improving, others declining during the treatment.^{1,2}

The blood was drawn from either the brachial or radial arteries. It was handled under oil throughout the analytical procedure to prevent the loss of gases and was kept at a low temperature to prevent decomposition. The oxygen content of the atmosphere in the oxygen chambers was maintained at 50 to 60 per cent, and the temperature and humidity were held at comfortable levels, at 70° F. and 30 per cent relative humidity.

When patients showed a low percentage of oxygen saturation of the arterial blood, *i. e.*, a decrease in the ratio of oxygen content to oxygen holding capacity, this was usually increased, often markedly so, by breathing atmospheres high in oxygen. A normal control, S. S., who had a slightly low saturation, 92.5 per cent, showed a rise to 96 per cent saturation, whereas control L. K., who entered the oxygen chamber with a saturation of 95 per cent, showed no increase. The oxygen administration also failed to affect the oxygen saturation of blood in our 1 case of lobar pneumonia (III). This has been shown to occur by Stadie⁶ and by Binger and Davis,⁷ who interpret their results as showing that in such cases there may be consolidated portions of the lung in which the circulation is unimpaired but in which the blood is never exposed to air containing alveoli, an opinion in which we concur. In such lungs the complete saturation of the blood passing through the unimpaired portions of the lungs would be insufficient to increase appreciably the total oxygen content of the blood in the peripheral arteries, since a large proportion of the blood might be passing through the consolidated portion and into the arterial system with no increase in oxygen content whatever. The situation is analogous to a congenital heart defect in which venous blood intermingles with the arterial.

In the patients suffering with cardiac disease several instances were noted in which the percentage oxygenation of the arterial blood increased at first, but decreased again as the heart failure progressed, despite the continued administration of oxygen.

The carbon dioxid content of the blood of all subjects, including the normal controls, was markedly increased during treatment with oxygen, and often remained above the original level for some time after the patient returned to his normal environment. These results are in accord with those of Campbell,⁸ who found an increased carbon dioxid tension in the extracellular tissue fluids of animals subjected to an environment of air at several atmospheres

of pressure. Case VIII, a patient suffering from emphysema, is worthy of note. As is usual in this condition, she entered the oxygen chamber with the abnormally high blood carbon dioxide content of 77.5 volumes per cent, which value rose to the remarkably high level of 100 volumes per cent during oxygen administration.

In all subjects there was a general tendency for a drift of the hydrogen ion concentration of the blood toward more alkaline values during oxygen therapy, although several exceptions were noted.

Discussion. Similar qualitative chemical changes in the arterial blood accompanied oxygen therapy in all individuals studied, including the normal controls. The changes differed markedly in degree in various individuals and conditions, but always in the same direction, thus emphasizing the fact that the effects of oxygen therapy are exerted upon the patient, rather than upon the disease. The administration of oxygen must be regarded as treatment to relieve the arterial anoxemia.

In some of the patients with heart disease there occurred at times clinical retrogression, which was paralleled by a decrease in blood oxygen saturation despite oxygen administration. It, therefore, seems logical to conclude that the oxygen cannot be considered as acting on the underlying cause of the disease. The function of oxygen therapy is to give the patient the benefit of as high a blood oxygen saturation as possible, while other means are employed to attack the underlying disorder.

It is interesting to note that all the hyperthyroid cases and one of the supposedly normal controls showed a percentage oxygen saturation of the arterial blood below the limits usually considered to be normal. This may be explained, in the hyperthyroid cases at least, as being due to an excessively rapid passage of blood through the lungs in such patients. The rapid flow shortens the time of exposure of the blood in the lungs to the alveolar air (this has also been alluded to by Binger, Brow and Branch⁹). An abnormal resistance to the passage of oxygen through the alveolar wall, or a lowering of the oxygen carrying power of the blood due to some chemical change of the hemoglobin may cause such a decrease in saturation.

The CO_2 and pH changes observed by us are similar to those reported by others. According to the view generally accepted at present and recently summarized by Barach³ they are to be regarded as secondary to respiratory changes produced by effects on the respiratory center. It must be pointed out, however, that Cullen *et al.*¹⁰ have recently questioned this point of view.

Conclusion. The function of oxygen therapy is not to attack the underlying causes of the disease, but to give the patient the benefit of as high a blood oxygen saturation as possible. It is conceivable, as was pointed out in a previous report,² that some of the benefits

of oxygen therapy may be produced in other ways besides the improvement of arterial anoxemia. However, the major benefit of oxygen therapy is the increase in oxygen saturation of the arterial blood, thus relieving the arterial anoxemia and its effects.

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BIBLIOGRAPHY.

1. Hamburger, W. W., Katz, L. N., Cohn, D. J., and Rubinfeld, S. H.: Observations on the Effects of Oxygen Therapy: I. Clinical Observations in Heart Disease, *J. Am. Med. Assn.* 1932, 98, 1779.
2. Katz, L. N., Hamburger, W. W., and Rubinfeld, S. H.: Observations on the Effects of Oxygen Therapy: II. Changes in the Circulation and Respiration. (Preceding article in this number.)
3. Barach, A. L.: The Therapeutic Use of Oxygen in Heart Disease, *Ann. Int. Med.*, 1931, 5, 428.
4. Barach, A. L., and Richards, D. W., Jr.: Effects of Treatment with Oxygen in Cardiac Failure, *Arch. Int. Med.*, 1931, 48, 325.
5. Levy, R. L., and Barach, A. L.: The Therapeutic Use of Oxygen in Coronary Thrombosis, *J. Am. Med. Assn.*, 1930, 94, 1363.
6. Stadie, W. C.: The Treatment of Anoxemia in Pneumonia in an Oxygen Chamber, *J. Exp. Med.*, 1922, 35, 337.
7. Binger, C. A. L., and Davis, J. S., Jr.: The Relation of Anoxemia to the Type of Breathing in Pneumonia: A Study of Respiration by Means of a Body Plethysmograph, *J. Clin. Invest.*, 1928, 6, 171.
8. Campbell, J. A.: Prolonged Alterations of Oxygen Pressure in the Inspired Air with Special Reference to Tissue Oxygen Tension, Tissue Carbon Dioxide Tension and Haemoglobin, *J. Phys.*, 1927, 62, 211.
9. Binger, C. A. L., Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing. I. Tachypnea, Independent of Anoxemia, Resulting from Multiple Emboli in the Pulmonary Arterioles and Capillaries, *J. Clin. Invest.*, 1924, 1, 127.
10. Cullen, G. E., Harrison, T. R., Calhoun, J. A., Wilkins, W. E., and Tims, M. M.: Studies in Congestive Heart Failure: XIII. The Relation of Dyspnea of Exertion to the Oxygen Saturation and Acid-Base Condition of the Blood, *J. Clin. Invest.*, 1931, 10, 807.

OVARIAN FOLLICLE HORMONE THERAPY IN OVARIAN INSUFFICIENCY AND THE MENOPAUSE.

BY BRUCE WEBSTER, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK.

THERE exists at the present time considerable confusion as to the status of ovarian hormone therapy. Rational as ovarian substitution therapy may theoretically appear to be in some conditions, the actual results are rarely striking and often difficult to detect. To some extent this is due to the lack of an objective index of ovarian activity. To this must be added the uncertainty of determining when the case is one of a pure ovarian insufficiency and when it is an anterior pituitary dyscrasia. There is some very convincing evidence as to the efficacy of substitution therapy in experimental ovarian insufficiency in animals. Here, however,

one is dealing with pure physiologic insufficiencies and not with the complex clinical syndromes which are encountered in clinical cases. Then, too, the quantities of hormone usually administered to experimental animals are relatively much greater than those ordinarily given to humans.

There have appeared from time to time convincing reports of the effect of various preparations of the ovarian follicle hormone in conditions of ovarian insufficiency. However, after carefully weighing the evidence regarding the efficacy of such therapy, a committee of the Council of Pharmacy of the American Medical Association decided that, although certain ovarian preparations were shown to be physiologically active, and able to induce œstrus in spayed animals, their therapeutic activity in the human, and their clinical field of usefulness, had not been sufficiently defined.

Since the isolation by Allen and Doisy¹ of the active hormone from the ovarian follicle, scattered clinical reports have appeared in the literature regarding the efficacy of this hormone in clinical subjects. McClendon² described 2 carefully studied patients in which he induced menstruation with the follicular hormone. Pratt³ reported a limited series of cases, which he considered to be true ovarian insufficiency, in whom he obtained beneficial results from the administration of a form of this hormone.

Hirst,⁴ Frank,⁵ Sevringhaus and Evans,⁶ Brouha and Simonnet,⁷ Mahnert,⁸ and Zondek⁹ have all given similar reports as to the beneficial effects of various preparations in a small series of cases. Novak¹⁰ is pessimistic about such therapy because of the difficulties of obtaining a satisfactory index of treatment. He further argues that the bleeding induced by such a method is not true menstruation.

Because of this diversity of opinions, the average clinician is hesitant to thrust such treatment upon his patients, in spite of the frequency with which he encounters conditions which appear to be true ovarian follicular hormone insufficiency. In view of the rapidly accumulating experimental evidence of the value of various preparations of this hormone, it seemed advisable to study the effect of a known physiologically active preparation in a series of clinical conditions which were commonly regarded as being due to ovarian insufficiency, with a view to substantiating further the work of previous observers, to determine some idea of the necessary dosage in terms of Allen-Doisy units, and to eliminate, as far as possible, all question of any benefits which might occur, being due to coincident nonspecific therapy.

The patients used in the following experiments were all ambulatory clinic cases. Only intelligent, coöperative women were chosen. These were seen at regular intervals throughout the period of observation. Two types of cases were selected for treatment: (1) menopause and (2) primary amenorrhea. Of the 10 cases of

menopause 2 were artificial and 8 were natural. All were selected because of the severity of symptoms such as hot flushes, pruritus, headache and nervousness. Cases with complicating hypertension were not used. In the 10 cases of amenorrhea there was considerable variation as to type, but all were shown to be free from anatomic lesions of the genital tract. Although pituitary ovarian insufficiency is not well defined, and it is difficult to determine which is primarily at fault, it soon became apparent that this group of cases could be divided into two clinical types. The first of these two types was anatomically normal in appearance, whereas the second showed obesity, hypertrichosis with masculine distribution, coarse voice and short stubby fingers. The first type was regarded as simple ovarian follicle hormone insufficiency, whereas the second was considered as belonging to the anterior pituitary ovarian dysfunction syndrome.

The ovarian follicular hormone used was prepared according to Morrell's modification of the Allen-Doisy technique.¹¹ The unitage of each batch was checked in our own laboratory in spayed rats, by the vaginal smear method.¹² The hormone was administered by means of vaginal pessaries, as described by Powers, Vanley and Morrell,¹³ and Allen and Baker.¹⁴ The dosage used varied considerably. In general, the principles of beginning with an overdose and diminishing it to the physiologic one was used. This appears to require adjustment in each individual case. During the control periods pessaries of plain gelatin were used and the patients were not informed of the change. No medication, other than the specific hormone, was given throughout the course of the study.

Table 1 is a summary of the cases used in the experiment. An effort was made to make the evaluation of results as critical as possible.

TABLE 1.—SHOWING THE RESULTS OF TREATMENT WITH OVARIAN FOLLICLE HORMONE.

	No. of cases.	Good results.	Fair result.	Doubtful result.	No relief.
Menopause:					
Natural	8	3	3	1	1
Artificial	2	2			
Amenorrhea:					
Ovarian follicle insufficiency	5	4	1		
Anterior pituitary ovarian type	5	5

The following case abstracts have been selected as being typical of the various groups described in Table 1. Examples of protocols in which no results were obtained have been included, as well as those in which good therapeutic effects were noted.

Case Abstracts. Group A. Natural Menopause. CASE 1.—C. P. (Cornell Clinic, A69034), American, white female, single, aged 41 years,

was admitted to the experimental group, February 17, 1931, complaining of nervousness, hot flushes, headache and cessation of menstrual periods. The patient had always been healthy. She was a business executive and indulged in athletics. Menses began at the age of 13 years and were always regular until the summer of 1930, when they became irregular and finally ceased in July, 1930. There was a gain of 20 pounds in weight in the 6 months prior to February, 1931. Physical examination showed no abnormal findings. There was moderate overnutrition; weight, 136 pounds. Systolic blood pressure was 140 and the diastolic 90. Pelvic examination was negative. A diagnosis of menopausal syndrome of only moderate severity was made.

Treatment. On February 17 the patient began to use intravaginally 300 Allen-Doisy units of follicular hormone daily. This was continued until February 21. On February 22 what appeared to be a normal menstrual period occurred and lasted 1 week. During this time the patient lost 5 pounds in weight. No hormone was administered until March 10, when she began to use 40 units daily. This was continued until March 22. No bleeding occurred although the patient volunteered the information that she had less headache and no flushes during the period of medication. From April 7 until April 30, 40 units of the hormone were used daily. On May 1 uterine bleeding occurred and lasted for 5 days. Treatment was discontinued until May 26, when the 40 units daily were begun. Bleeding again took place on June 1. Treatment was discontinued. No period occurred in July. The experiment was terminated on July 2. The patient then weighed 122 pounds. She stated that she had more energy and was almost free from symptoms during the time period when she was using the follicular hormone. This patient was a highly intelligent individual and insisted that the benefit was not psychic.

A reply to a follow-up letter was received on December 16, 1931. The patient stated that she was without therapy during June and July. About July 15 she had a return of her symptoms, such as flushes, nervousness and headache. These continued until she began using the hormone again on August 22. A menstrual period occurred on August 28. She had continued to use approximately 200 units during the last week of each intermenstrual period. Under this régime she had remained symptom free and had had what she considers to be regular menstrual periods.

Result. Reestablishment of uterine bleeding in a case of recent menopause with relief of symptoms and a loss of 10 pounds in weight after moderately large doses of ovarian follicular hormone. On discontinuing treatment during a control period the symptoms reappeared and monthly uterine bleeding did not take place.

CASE 2.—P. H. (Cornell Clinic, A74075), Russian female, married, aged 48 years, was admitted to experimental group on February 16, 1931, complaining of hot flushes, and cessation of menses. The past history was negative. The menstrual periods were regular until 1928. They then were irregular for 6 months and ceased in 1929. Since that time she had had severe hot flushes, occurring every 20 to 30 minutes, and aggravated by excitement. There had been a gain of 20 pounds in weight during the past 3 years. Physical examination was normal except for a slight laceration of the pelvic floor. The systolic blood pressure was 140 and the diastolic 86. The diagnosis was menopausal syndrome, moderately severe.

Treatment. On February 24 the patient began to use 40 Allen-Doisy units of follicular hormone daily. On March 10 she volunteered the information that flushes were occurring less often; on March 24 the flushes occurred only 6 to 8 times per day and were much less severe. On March 24 blank gelatin pessaries were substituted for those containing the hormone. On March 31 the patient complained of increased severity and frequency

of the flushes; on April 4 she began using 40 units of the hormone every second day; on April 14 she again noted a decrease in the frequency and severity of the flushes. Treatment was continued until June 9. The flushes continued to occur every 6 to 8 hours but were not severe. No menstrual bleeding occurred. There was no change in body weight or blood pressure.

Result. Moderate relief of subjective symptoms only in a case of menopausal syndrome of 2½ years' duration. The general result of therapy was considered doubtful in this case, although the patient had so much symptomatic relief that she desired to continue the treatment after the termination of the experiment. An attempt was made to determine the condition of the patient on December 15, 1931, but she could not be found.

Group A. Artificial Menopause. CASE 3.—M. L. (Cornell Clinic, A70742), white female, single, aged 42 years, was admitted to the experimental group on December 2, 1930, complaining of severe hot flushes. The past history was negative until March, 1930. At that time the uterus and both ovaries were removed because of multiple cysts in the latter. The menses, which had been regular until the operation, did not occur after it. Two weeks postoperatively she began to have severe hot flushes which were accompanied by palpitation and sweating. These were so severe that she was forced to stop her work as a secretary. They occurred at intervals of from 1 to 2 hours. During September and October, 1930, she took 15 grains of dried ovarian substance daily without effect. Physical examination revealed a healthy looking, intelligent woman with no abnormal findings. The systolic blood pressure was 150 and the diastolic 86. The diagnosis was menopause, artificial, severe.

Treatment. On December 2, 1930, the patient began to use 40 units of the follicular hormone intravaginally daily. On December 16 no change in condition was noted. On January 7, after using 40 units daily for 1 month, she volunteered the information that she had for the past 3 or 4 days noted a striking change in her condition. The flushes were much less severe and were no longer accompanied by palpitation and sweating. On January 14 she complained of a fullness in her breasts. Examination showed both breasts to be firm and tender. The flushes now occurred only occasionally and were not troublesome. The dosage of 40 units daily was continued until March 3. The patient remained almost symptom free. There was no change in blood pressure or body weight. On March 3 blank gelatin pessaries were substituted for those containing the hormone. She remained free from symptoms until March 20, when she began to have a return of the flushes and felt much as she did before beginning treatment. On March 25 she began to use 40 units of the hormone every second day; on April 7 she reported that she was again free from symptoms. This dosage of 40 units every second day was continued until June 1. During this time the patient remained without symptoms and carried on with her work. On June 1 the dosage was reduced to 40 units every third day. This proved to be sufficient to keep her symptom free. On July 1, at the termination of the experiment, the systolic blood pressure was 160 and the diastolic 86. There was no change in weight. A letter was received from the patient on December 16, 1931, in which she stated that 80 units per week were necessary to keep her free from symptoms. On several occasions she had tried reducing the dose but found that the flushes began to occur each time this was attempted.

Result. Striking relief of symptoms occurred in a case of artificially induced menopause. A return of symptoms took place during a control period when the hormone was stopped. A follow-up letter 1 year after the beginning of the experiment elicited the reply that the patient was continuing the therapy and was still free from symptoms.

Group B. Amenorrhea, Ovarian Follicle Insufficiency Type. CASE 4.—J. K. (Cornell Clinic, A59059), English school girl, single, aged 16½ years, was admitted to experiment on December 2, 1930, complaining of weakness and the fact that she had never menstruated. The past history was negative. The patient had never been robust and had received careful medical attention all her life. From time to time she had taken large quantities of dried ovarian substance by mouth, with no evident effect. Physical examination revealed a normal looking, slightly undernourished girl. Nothing abnormal was found. The lungs were clear and an intracutaneous tuberculin test was negative. Rectal examination revealed a small uterine fundus and cervix. The diagnosis was amenorrhea.

Treatment. On December 2 the patient began using 40 units of ovarian follicular hormone every second day intravaginally. On December 5 uterine bleeding occurred and lasted until December 9. This was the first occasion on which the patient had noted any evidence of menstruation. She continued to use 40 units every second day. On January 6 a second period occurred and lasted until January 10. It was accompanied by some abdominal pain. The therapy was stopped at this time, and blank pessaries substituted. On February 10 no further periods had occurred. At this time 40 units every third day was begun. On April 16 bleeding began and lasted for 4 days. The same dosage was continued and another period occurred on May 17 and lasted for five days. On June 1 the experiment was terminated.

The patient's mother replied to a follow-up inquiry on December 2, 1931. From June until the end of September the patient used 40 units of the ovarian follicle hormone twice weekly. Menstrual bleeding continued to occur at regular intervals. In October the therapy was stopped and a period occurred during October and again in November. Her general condition remained satisfactory.

Result. Menstrual bleeding at regular intervals occurred for the first time in a girl, aged 16½ years, during the administration of 80 units of the ovarian follicular hormone every second day and ceased to occur when therapy was withheld, during a control period. After 10 months of treatment with the hormone, it was discontinued and regular menstrual periods occurred for 2 months after therapy was stopped.

CASE 5.—L. A. (Cornell Clinic, A25605), Russian female, married, aged 24 years, was admitted, November 11, 1930, complaining of gain in weight and irregular menstruation. General health had been good. Menstruation began at the age of 15 years and had always been irregular. Periods usually occurred once every 3 or 4 months, were accompanied by dysmenorrhea and were scanty. The last period was in September, 1930. The patient had been married for 3 years. Frigidity existed. No pregnancies had occurred, although the husband had been shown to have active spermatozoa and no contraceptives were used. There had been a gain of 20 pounds in weight during the past 2 years. Physical examination showed an overweight, healthy looking young woman. Nothing abnormal was found in the general physical examination. The uterus was of the infantile variety and the cervix was small. There was no hypertrichosis and the hair distribution was of the normal feminine type. Diagnosis was amenorrhea, of ovarian follicle insufficiency type.

Treatment. On November 25 the patient began to use 40 units of the ovarian follicular hormone daily. This was continued until January 25, 1931. In all, approximately 2400 units were used. No menstruation occurred, but on January 25 the patient had severe abdominal cramps of the variety which she always associated with her menstrual periods. On February 1 she began using 300 units daily. On March 3 a menstrual period began which lasted until March 10. The blood loss was copious

and there was considerable pain. The patient stated that this was the first time she had ever experienced a menstrual period of that duration. No treatment was given until March 24, when she again began to use 40 units of the follicular hormone daily. Slight bleeding occurred on April 21 and a normal period of 6 days' duration began on April 28. There was very little dysmenorrhea on this occasion. Therapy was stopped until May 20, when she began to use 40 units daily. A period occurred on June 2 and lasted 5 days.

On June 15 there was no change in the patient's physical condition except for a loss of 7 pounds in weight. Her mental attitude was very much improved.

In a follow-up interview on December 2, 1931, the patient stated that she continued to use 40 units of the ovarian follicle hormone daily for 10 days preceding the usual date of the onset of menstruation throughout June, July, August and September. During this time the menstrual periods continued to be regular and she lost weight steadily. For financial reasons she was forced to discontinue the therapy at the end of September. No menstrual bleeding had occurred since and she had begun to gain in weight.

Result. Regular menstruation appeared to have been established in a woman, aged 24 years, in whom menstruation had previously been grossly irregular. Approximately 12,000 units of the hormone were used before menstruation became established. Relatively small quantities apparently were sufficient to maintain the menstrual cycle once it was established. After 7 apparently normal menstrual periods therapy was stopped because of the expense and no periods occurred.

Group B. Amenorrhea, Anterior Pituitary Type. CASE 6.—D. S. (Cornell Clinic, A69345), Russian female, aged 16 years, was admitted to experimental group, November 25, 1930, complaining of short stature and absence of menstruation. The child was normal at birth but had always grown slowly. The parents were normal. During the past year she had gained 15 pounds in weight. No menstrual periods had occurred. Physical examination showed a short, obese person, height 50 inches and weight 86 pounds. The fat was evenly distributed. The hands and feet were relatively small and the fingers were short. Body hair was sparse. Rectal examination revealed an infantile type of uterus and cervix. No other gross physical abnormalities were present. The diagnosis was anterior pituitary ovarian dysfunction.

Treatment. From November, 26, 1930, until February 15, 1931, the patient used 40 units of ovarian follicular hormone daily. At the end of that time no menstrual periods had occurred and there was no change in body weight. From February 1 to February 7 she had severe abdominal cramps. These disappeared and did not recur. During the month of March 4000 units of the hormone were administered. No demonstrable change occurred. On May 1 physical examination revealed essentially the same findings as on admission. There was no change in body weight or height.

A reply to a follow-up letter was received on December 10, 1931. The patient's mother stated that the girl had had no menstrual bleeding and that there had been no change in her condition except a slight gain in body weight.

Result. No effect was noted after the administration of approximately 7000 units of the ovarian follicular hormone in a girl of 16 years, who showed the physical characteristics usually interpreted as being due to anterior pituitary ovarian disturbances. The amenorrhea persisted.

CASE 7.—E. S. (Cornell Clinic, A69382), Jewish female, married, aged 36 years, was admitted to experimental group on December 9, complaining of lack of menstruation. Patient had always been healthy. Two scanty

menstrual periods had occurred at the age of 15 years. There had been none since then. She had been married for the past 5 years and no pregnancies had occurred. Her husband had been shown to have active spermatozoa.

Physical examination showed a healthy looking woman. Weight, 138 pounds. There was increased hair growth of the face and legs and the abdominal distribution of hair was of the masculine variety. The hands and feet were large. The uterus and cervix were small and of the infantile type. The diagnosis was amenorrhea of anterior pituitary ovarian type.

Treatment. Between December 9 and March 9 the patient used 4000 Allen-Doisy units of the follicular hormone. No menstrual bleeding or abdominal cramps occurred. There was no change in body weight.

Result. Four thousand units of the hormone distributed over a 3 months' time period produced no effect in a woman, aged 36 years, with anterior pituitary ovarian dysfunction.

Discussion. Strikingly beneficial results were obtained in 3 of the 8 cases of natural menopause treated with ovarian follicular hormone. In each of these 3 instances the menopause was of less than 1 year's duration. In these cases there was marked relief of symptoms and reestablishment of uterine bleeding. It is fully realized that there is no particular benefit to be gained by reestablishing uterine bleeding after the menopause has set in. In the present experiment it was simply regarded as evidence that the hormone was physiologically active and capable of producing an effect which could not be considered psychic in these cases. All 3 of these individuals showed partial loss of excess weight. In 3 of the 5 cases in which the menopause was of 2 to 5 years' duration, there was considerable symptomatic relief but no return of menstrual bleeding after treatment. These results were classified as "fair," since it is recognized that any form of therapy, and especially the so-called "glandular therapy," can have a striking psychic effect on this type of case. There did appear, however, to be considerable relief from the "hot flushes" in these individuals. These had been a most distressing symptom in all of the cases. A variable length of time after treatment was begun the patients noted a definite diminution in the frequency and duration of the flushes. In 3 cases they stopped occurring. In 1 instance, however, even after several thousand units of the hormone, there was no symptomatic relief.

The 2 cases of artificial menopause both obtained what appeared to be remarkable relief from headaches, hot flushes and nervousness. In both instances this result did not manifest itself until nearly 1000 units had been used. The relief continued for approximately 1 week after therapy was stopped during a control period. At the end of that time the symptoms returned and persisted until the hormone was again started. In 1 individual, marked congestion of the breasts was noted after using relatively large quantities of the hormone. These 2 cases of artificial menopause could be maintained symptom free on approximately 500 units of the hormone each per month. No definite effect on the blood pressure was noted

in any of the cases during the period of hormone administration. There was a loss of 10 pounds or more in weight, in the course of the 3 months' duration of the experiment, in 6 of the 10 cases.

The cases of amenorrhea which were regarded as being due to simple follicle hormone insufficiency responded well to substitution therapy. Cases 4 and 5 have been selected as typical examples of this group. In striking contrast are Cases 6 and 7, in which no response occurred in spite of the administration of several thousand units of the hormone. These 2 latter cases exemplify a group which is usually regarded as being due primarily to anterior pituitary dyscrasia. Their lack of response to the follicle hormone confirms this classification.

Conclusion. A series of 20 cases is presented in which the intravaginal administration of the ovarian follicle hormone has been alternated with control periods. It would appear that the preparation of the hormone used was physiologically active in humans, as evidenced by the induction of uterine bleeding. Further, data are presented which suggest that this hormone of the ovarian follicle is of definite clinical therapeutic value in the treatment of the disagreeable symptoms which may accompany the menopause and of the amenorrhea due to an insufficiency of that hormone. No beneficial results were obtained when the hormone was administered to cases of amenorrhea which showed clinical evidences of an anterior pituitary etiology.

REFERENCES.

1. Allen, E., and Doisy, E. A.: Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification and Action in Test Animals, *J. Am. Med. Assn.*, 1923, **81**, 819.
2. McClendon, J. F., Burr, G., and Wildebush, F. F.: Induction of Menstruation in Women by Use of Ovarian Hormone, *Proc. Soc. Exp. Biol. and Med.*, 1929, **26**, 430.
3. Pratt, J. P.: Abstract of Discussion of Paper by Edgar Allen: Endocrine Activity of the Ovary, *J. Am. Med. Assn.*, 1931, **97**, 1189, 1192.
4. Hirst, J. C.: Clinical Use of Ovarian Follicular Hormone With Special Reference to Functional Sterility, *Am. J. Obst. and Gynec.*, 1928, **15**, 487.
5. Frank, R. T.: Endocrine Therapy, *Am. J. Obst. and Gynec.*, 1928, **15**, 40.
6. Sevringhaus, E. L., and Evans, J. S.: Clinical Observations on Use of Ovarian Hormone: Amniotin, *Am. J. Med. Sci.*, 1929, **178**, 638.
7. Brouha, L., and Simonnet, H.: Action of Graafian Follicle Liquid Extract on Mature Female Rats, *Compt. rend. Soc. de biol.*, 1925, **93**, 557.
8. Mahnert, A.: Der monatliche Zyklus und seine hormonale Beeinflussung, *Wien. klin. Wchnschr.*, 1928, **41**, 329.
9. Zondek, B.: Das Ovarialhormon und seine klinische Anwendung, *Klin. Wchnschr.*, 1926, **5**, 1218, 1521.
10. Novak, E.: Functional Disorders of Menstruation, With Remarks on Organotherapy, *J. Am. Med. Assn.*, 1930, **95**, 1221.
11. Morrell, J. A., McHenry, E. W., and Powers, H. H.: Distribution and Preparation of Ovarian Follicular Hormone, *Endocrinology*, 1930, **14**, 25.
12. Long, J. A., and Evans, H. M.: Oestrous Cycle in the Rat, *Mem. Univ. California*, 1922, **6**.
13. Powers, H. H., Varley, J. R., and Morrell, J. A.: Preliminary Note on Assay of Follicular Hormone by Vaginal Administration, *Endocrinology*, 1929, **13**, 395.
14. Allen, E., and Baker, D. D.: Menstrual Periods Induced in Ovariectomized Monkeys by Estrus Producing Ovarian Hormone, *Am. J. Obst. and Gynec.*, 1930, **20**, 85.

HYPERPERISTALTIC ELECTROGRAPHIC EFFECTS.*

BY I. HARRISON TUMPEER, S.M., M.D.,

ASSOCIATE ATTENDING PEDIATRICIAN, MICHAEL REESE HOSPITAL,

WITH THE TECHNICAL ASSISTANCE OF

BESSIE PHILLIPS,

ELECTROCARDIOGRAPHIC TECHNICIAN, HEART STATION, MICHAEL REESE HOSPITAL,
CHICAGO.

(From the Sarah Morris Hospital for Children and the Heart Station of Michael Reese Hospital.)

THE usefulness of the electrocardiogram in the diagnosis of conduction disturbances of the heart by portraying the nature, direction, sequence and timing of the cardiac stimulation suggests the application of the electrocardiographic method to the other common type of rhythmic activity represented by gastrointestinal peristalsis. The basis of both manifestations is the action current incident to the muscle contraction. Direct electrogastrography has been performed by Alvarez¹ and Alvarez and Mahoney² in cats by the use of a modified d'Arsonval galvanometer and small calomel electrodes made up with Locke's solution clamped against the bowel wall with small wooden clamps. Simultaneous mechanograms corresponded with the electrograms. In 1922 Alvarez³ succeeded in obtaining a record in the human by placing electrodes directly on the abdominal wall of an emaciated old woman with visible peristalsis. He failed to duplicate these findings in better muscled subjects.

The Present Problem. It had long been considered that the visible peristalsis accompanying congenital hypertrophic pyloric stenosis offered a favorable opportunity for electrographic registration because such vigorous muscle contraction must necessarily develop strong action currents and positive results could be checked visually. Opposed to this idea, the impression has been current that the peristaltic action current is too slow to be recorded by the ordinary string galvanometer.

In the first attempts to obtain electrograms of gastric peristalsis mesh electrodes fitting the curvature of the baby's abdomen were applied in the regions corresponding to the fundic and pyloric portions of the stomach. The ordinary Hindle galvanometer was used, and a preliminary announcement was made in 1926.⁴ Objections may be offered to direct abdominal leads on account of the possible artefacts produced by mechanical shifts in the position of the electrodes, a distortion aggravated by respiratory movements. Subsequently, the indirect or ordinary electrocardiographic leads

* Aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

were employed because this procedure would avoid the objections to the direct leads and because the former would afford a norm, deviations from which associated with visible peristaltic waves might justly be ascribed to these contractions. In other words it was presumed that hyperperistalsis like skeletal muscle contraction would develop sufficient action current to interfere with or alter the known constant, viz., electrocardiogram. Furthermore, indirect leads enjoy the advantage of ease of application. It is more practicable to keep the baby quiet with electrodes attached to the extremities, and records merely require patience to achieve a state of quiet in the child. Lead III was arbitrarily chosen and was continued throughout the observations because it yielded positive results at once.

Records were obtained from 2 infants with congenital hypertrophic pyloric stenosis presenting readily visible gastric peristalsis. Intestinal peristalsis was recorded in an infant with congenital hypertrophic dilatation of the colon (Hirschsprung's disease) whose peristaltic waves rushed over the abdomen in different directions simultaneously. In the course of this tracing an unexpected curve appeared without visible peristalsis or other movement of the child. Upon investigation it was found that the infant had extruded a stool, by rectal peristalsis apparently. Finally, in connection with intestinal peristalsis an unusual record will be introduced: it was obtained in the course of a routine electrocardiographic examination of a patient with audible peristaltic rumblings.

Gastric Hyperperistalsis. CASE 1.—R. F., aged 5 weeks, male, first born, birth weight 7 pounds 7 ounces, was admitted to the Sarah Morris Hospital, March 30, 1931, weighing 8 pounds. He had been under observation since the age of 2 weeks when symptoms of stenosis first became evident. On admission, the typical picture presented consisting of projectile vomiting following ingestions of feedings and water, scanty stools, scanty urine, stationary weight terminating in loss, visible gastric peristalsis and tumor palpable to the right of the umbilicus. The diagnosis of obstruction was confirmed by radiological examination, and surgical exposure revealed a large hypertrophic pyloric tumor. The electrogram was obtained preceding operation.

Comment. The alteration of the normal level base line of the electrocardiogram manifested by a wavelike shift occurs simultaneous with the peristaltic wave. More specifically, the noticeable change occurred when the visible wave approached the midline of the abdomen in its right-sided progress. It was our practice to notify the technician at the outset of the peristaltic bulge in the left hypochondrium, but she reported no marked deviation of the string until we found the wave had reached the midarea. When the procedure was reversed the technician invariably reported the change in the string when the observer noted the wave well advanced to the midline. This observation confirms the findings of Alvarez. In his experiments on the exposed stomach the wave seemed to arise about

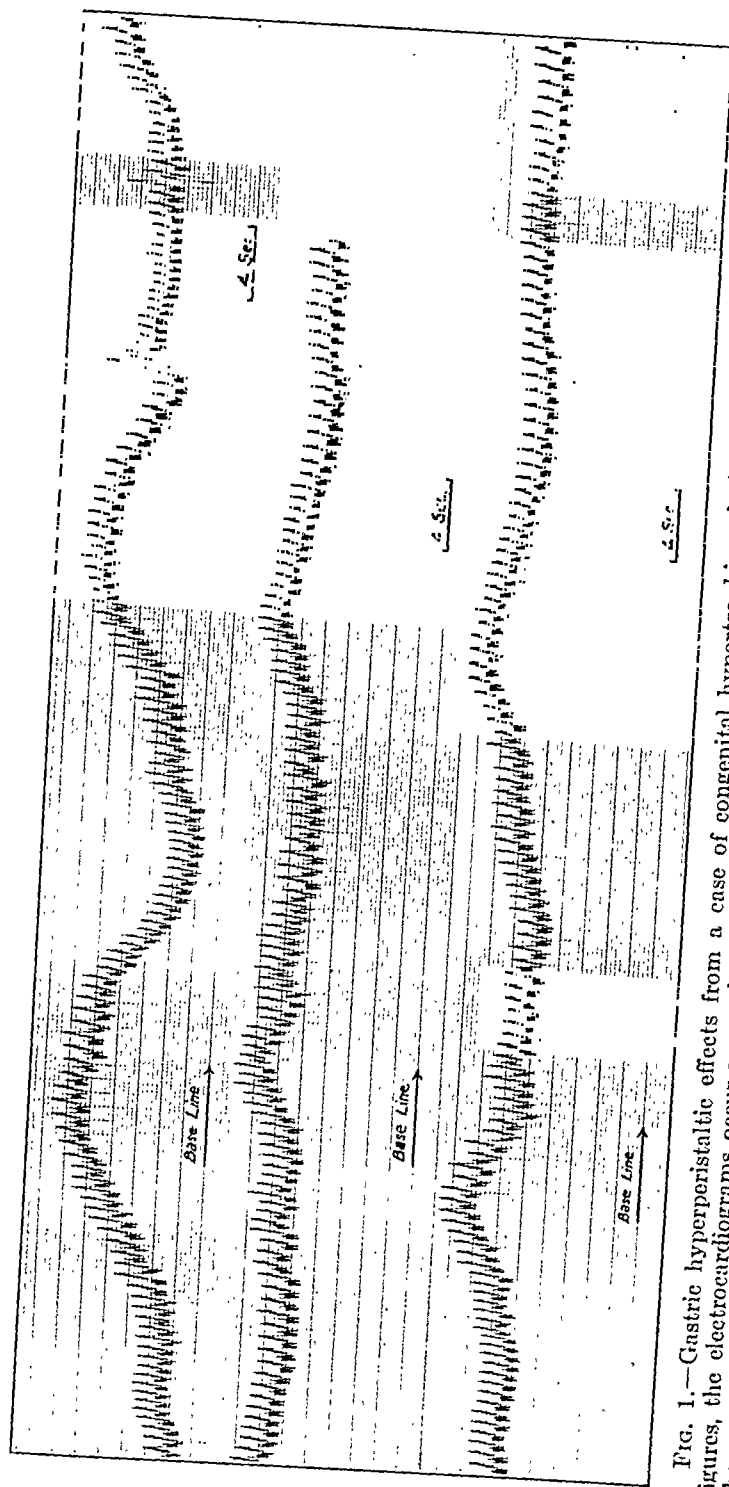


FIG. 1.—Gastric hyperperistaltic effects from a case of congenital hypertrophic pyloric stenosis. In this and the following figures, the electrocardiograms occur as usual. The peristaltic effects are represented by excursions from the base line. Note the camera is slowed to $\frac{1}{6}$ of the normal rate. The normal rate was used in Figs. 2 and 3, the earlier records.

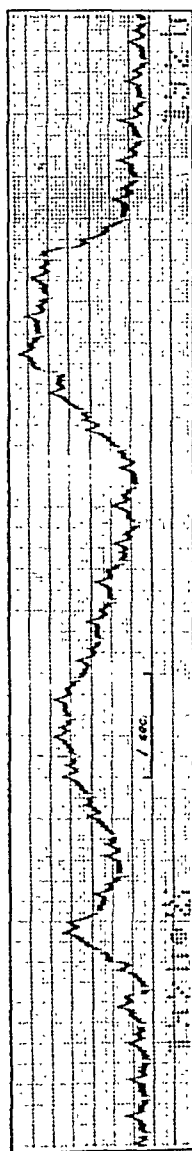


FIG. 2.—Intestinal hyperperistaltic effects from a case of congenital hypertrophic dilatation of the colon (Hirschsprung's disease).

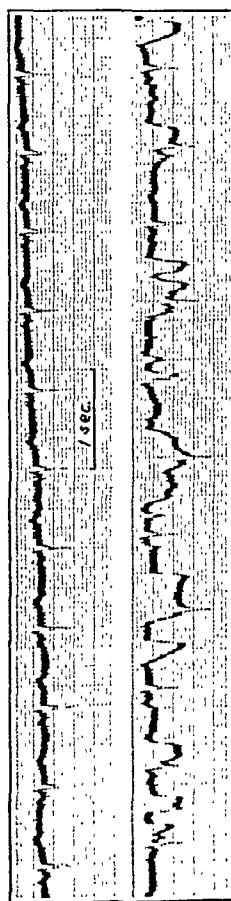


FIG. 3.—Borborygmie effects (irregular and arrhythmic) obtained during the routine electrocardiographic examination of a patient with cardiac symptoms. The upper strip was obtained during quiescence. The lower strip was recorded during the same session coincident with active, audible peristaltic rumblings.

the middle of the stomach. The lag in the electrographic record may be explained on the basis of the summation of current which manifests itself maximally or optimally with regard to the cardiac current at the mid-position of the peristaltic wave. The peristaltic disturbance as evidenced by the curves in the electrocardiographic base line occurs at the rate of three per minute, a duration of 20 seconds. This agrees with the frequency of gastric peristaltic action as judged by the rise in intragastric pressure determined by the balloon method⁵ and likewise found by Alvarez.

Intestinal Hyperperistalsis. CASE 2.—N. S., aged 3 years, female, was admitted to the Post Graduate Hospital, October 17, 1924 for feeding difficulty and retarded development since birth and abdominal distention particularly conspicuous for the past year. Briefly, the child presented an emaciation characteristic of a dystrophy of long standing, and her color was sallow. The abdomen was greatly distended, sometimes hard and at other times quite soft. The coils of colon and their large peristaltic undulations passing under the abdominal wall were very striking. The tongue was the geographical type, and there were marked teeth grinding and finger movements. Radiographic examination by the opaque enema disclosed "a very much enlarged colon with not only a very great increase in circumference but also a marked redundancy in the length of the sigmoid loop which presented high up on the right side in the usual position of the cecum." The electrographic record was obtained November 24, 1924. Subsequently, a sigmoidectomy was performed with an end-to-end anastomosis. Death followed, and necropsy disclosed peritonitis.

Comment. This record reproduces frequent and irregularly timed changes in the base line occurring when the meandering colonic peristalsis resulted in currents physiologically adequate to interfere with the cardiac picture. The frequency and irregularity of interval and excursion in the intestinal type of peristalsis was predictable because these waves do not traverse a definite path across the abdomen like gastric waves. The hyperperistalsis in Hirschsprung's disease occurs commonly in several segments simultaneously and is due to the functional if not anatomical obstruction characteristic of this condition. Prominent as the frequency and irregularity appear in the record submitted, these factors are nevertheless minimized in comparison with the preceding gastric tracing because the latter was taken at less than one-sixth of the speed of the former. The intestinal record taken early in our observations was obtained without altering the speed of the regular cardiographic camera. Consequently, the breadth of the response is emphasized with reciprocal lessening of the base-line excursion in comparison with the picture reproduced by a slower camera. At the rate of the gastric curve, the intestinal record should be imagined one-sixth its length.

During the record a single wave occurred without visible accompaniment. Olfactory evidence testified to the passing of a stool readily confirmed by inspection. It is likely that the invisible rectal peristalsis was recorded as a single wave due to a single course of action current resembling the picture of gastric peristalsis.

CASE 3.—I. G., aged 54 years, was referred from the Mandel Clinic to the Heart Station for electrocardiographic examination on the basis of a history of dyspnea on exertion, hypertension, and seizures of angina pectoris. The records presented were obtained May 28, 1930. Three months later the patient was hospitalized for coronary disease. Death occurred September 17, 1930. No necropsy.

Comment. The circumstances attending the inclusion of this record are noteworthy. The bizarre electrographic records obtained in infants manifesting hyperperistalsis recalled to the technician the peculiar record obtained in a patient almost a year previously. During the course of a routine cardiogram she observed strange movements of the string. Leaving her recording room, she approached the patient to note and inquire whether an artefact had been produced. The patient was lying perfectly quiet, but she was struck by the sound of loud borborygmi emanating from him. She continued to take a strip of record during this period. It is a coincidence that Lead III which was used in our deliberate efforts, was connected at this time. The upper strip illustrated was obtained during a quiet period although there seems to be a slow shift in the base line even here. This was more conspicuous in Lead II (not reproduced). The lower strip was taken during the active, audible peristaltic rumblings. The interpretation of this record is peculiarly significant:

"May 28, 1930. Sinus arrhythmia. Rate average 82. *P-R* interval 0.14 seconds. *R* is slurred in Leads I and II and notched in Lead III. Left axis deviation. No evidence of myocardial abnormality other than left ventricular preponderance. (The other part of Lead III was taken during audible peristaltic rumblings. The ventricular complexes are unchanged. The rest of the bizarre tracing cannot be interpreted. Record of peristaltic wave?)"*

On two subsequent occasions this patient was examined with no reappearance of the "bizarre" finding. The electrocardiograms on these occasions resembled the previous typically cardiac record. The peculiar effect observed in this condition is likewise probably due to vigorous intestinal peristalsis, sufficiently active to produce loud borborygmi. It is presented as it stands as an unusual electrographic effect accompanying intestinal hyperperistalsis in the absence of other evident cause and resembling by its irregularity the effect produced by the other type of intestinal hyperperistalsis found in Hirschsprung's disease. The more rapid base line undulations in this record as compared with Fig. 2 may be explained on the basis of summations of distant synchronous peristaltic activity

* Since there was no clue to the tracing except that a notation of the rumbling in explanation of the curious curve had been appended to the diagnostic card and a strip of tracing had been preserved, it was necessary to search systematically through the records of the department to secure the data. About 6500 cards were examined before finding the record. In the meantime several thousand films had likewise been subjected to scrutiny. This yielded many records with suggestively shifting base lines.

due both to the larger size of the individual and the wider distribution of the activity.

Discussion. All results were obtained while the subject was quiet or asleep to avoid artefacts due to contraction of skeletal muscles. This proved easy in the child with Hirschsprung's disease. Many attempts in infants with pyloric stenosis failed because these babies are irritable unless markedly atrophic. The fretfulness is provokingly aggravated at the height of the peristaltic wave due to the pain or pressure. This has been noted by the author and others during observations on hunger contractions in infancy.⁶ Frequently, a spasm manifests itself in the facial expression of the infant asleep during the experiment. Sedatives were not used in this series to obviate objections to the results. However, sedatives not markedly affecting peristalsis should greatly facilitate observations of this kind. In this connection, an attempt to obtain a record during light ether anesthesia immediately preliminary to surgical correction in the operating theater proved a failure as predictable.

It is not claimed that the waves recorded are true reproductions of peristaltic waves. It should be appreciated that the electrocardiogram is not the record of individual impulses but represents merely the moving picture of the changing algebraic sums of innumerable action currents in innumerable anatomic portions of the heart running in different directions simultaneously.⁷ Similarly, the peristaltic "effect" is an electrogastrogram or an electroenterogram depending on the organ of origin and is merely the algebraic summation of innumerable action currents produced in a relatively long, more or less hollow viscus manifesting contraction waves preceded by inhibition waves and constantly changing its position.

Indirect and direct considerations testify to the authenticity of electrographic registration of peristaltic effects. From the indirect standpoint it is obvious from a study of the tracings submitted that these changes differ from artefacts due to skeletal muscle contraction and from respiratory interference. From the direct standpoint there is coincident visual evidence of unusually strong smooth muscle contraction. Furthermore, the result of gastric peristalsis is a rather regular wave to be expected in a movement following a definite direction, and its duration coincides with the time determined by mechanical methods of examination. Regularity in the intestinal record is lacking, likewise to be expected, because the anatomic distribution of the intestinal coil is irregular. Most gratifying to the confirmation of the above is the gratuitous check offered these findings by the unpremeditated and unprejudiced record of the patient with borborygmi.

It follows logically that peristaltic effects must manifest themselves as supposed artefacts in the countless records already gathered, but there is no reference to such effects. In a review of 15,600

records, Esler and White⁵ divide the artefacts into extrinsic and intrinsic depending on whether the cause lies within or without the subject. Smooth muscle effects or artefacts are not mentioned in their catalogue, but they conclude that the frequent electrical distortions demand more consideration than is usually accorded them. Shifts in the base line are frequently seen in electrocardiograms. Wenckebach and Winterberg⁹ published several electrograms presenting significant shifts incidental to a study of the effect of vagus pressure and other measures. It is conceivable that the base line shifts are due to peristalsis which vagus stimulation, at least, may produce. Furthermore, in the search through our files for the electrocardiogram presented in Fig. 3 many films were found with varying degrees of base line shifts. It is possible that some of these were peristaltic effects.

It is a curious commentary that although this study was undertaken to obtain electropéristaltograms, particularly electrogastrograms, it has resolved itself, in fact, to an elucidation of an electrographic effect due to hyperperistalsis.

Summary. An indirect electrographic record of gastric hyperperistalsis is presented.

The electrogram resembles the mechanogram in form and frequency.

Indirect electrographic records of intestinal hyperperistalsis are submitted from three types of intestinal activity.

The peristaltic effect on the electrocardiogram was predictable by nature of its contractile genesis.

It may be assumed that these effects have been previously recorded but have remained overlooked or misunderstood, since there is no previous record of this observation.

Further study should reveal a new field of fact in electrographic effects and peristaltic activity.

NOTE.—Acknowledgment is made of the valuable suggestions and criticism rendered by Dr. Louis N. Katz, Physiologist and Director of Cardiovascular Research, Michael Reese Hospital.

REFERENCES.

1. Alvarez, Walter C.: *Am. J. Physiol.*, 1922, 58, 476.
2. Alvarez, Walter C., and Mahoney, Lucille J.: *Am. J. Physiol.*, 1924, 69, 226.
3. Alvarez, Walter C.: *J. Am. Med. Assn.*, 1922, 78, 1116.
4. Tumpcer, I. Harrison, and Blitzsten, Pauline W.: *Am. J. Dis. Child.*, 1926, 31, 451.
5. Carlson, Anton Julius: *The Control of Hunger in Health and Disease*, Chicago, Illinois, The University of Chicago Press, 1916, p. 36.
6. Carlson, A. J., and Ginsburg, H.: *Am. J. Physiol.*, 1916, 39, 310.
7. Ginsburg, H., Tumpowsky, I., and Carlson, A. J.: *J. Am. Med. Assn.*, 1915, 64, 1822.
8. Katz, L. N., and Weiman, S. F.: *Am. J. Phys.*, 1927, 81, 360.
9. Esler, James W., and White, Paul D.: *Am. Heart J.*, 1929, 4, 296.
9. Wenckebach, K. F., and Winterberg, H.: *Die unregelmässige Herztätigkeit*, Tafelband, Leipzig, Verlag von Wilhelm Engelmann, 1927, Figs. 63, 79, 206, 318.

**PELLAGRA: IMPROVEMENT WHILE TAKING SO-CALLED
"PELLAGRA-PRODUCING" DIET.**

BY TOM DOUGLAS SPIES, M.D.,

TEACHING FELLOW IN MEDICINE,
WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO.

(From the H. K. Cushing Laboratory of Experimental Medicine and the Medical Service of Lakeside Hospital.)

For decades investigators have sought the cause of pellagra and to this date uniform agreement as to the etiologic factor is lacking.^{1,2,3} Important evidence has accumulated which suggests a deficiency in diet as a cause. Some investigators believe that the production of the clinical disease depends on a deficient diet plus some additional factor, perhaps infection.¹ It is of interest that the relationship of a poor diet to pellagra has been stressed since its earliest recognition. Goldberger and his coworkers^{3,4,5,6,7} have brought forward considerable evidence toward establishing pellagra as a dietary deficiency disease. They have described the production and the cure of pellagra in human beings by a means of dietary manipulation. They particularly associate the condition with lack of vitamin G (B₂). It seems fair to state that current opinion favors a dietary explanation of the disease.

The majority of the cases of pellagra observed in the northern part of the United States are associated with chronic alcoholic intoxication. The nature of the relationship of alcohol to the development of the disease is a moot question. It is certain that pellagra occurs in people who do not drink. In some instances a relationship between alcoholic debauches and the development of the disease seems assured. The majority of workers feel that repeated indulgence in alcohol at times prevents an adequate food intake, thus favoring the production of pellagra. Regardless of the difference of opinion concerning the relationship of true pellagra to postalcoholic dermatitis, the lesions in the two conditions appear identical.

Many drugs, minerals and diets have been proposed as a cure for this disease. Inevitable controversy has arisen as to their efficacy. Since pellagra is such a variable disease, it seemed especially worthwhile to study the acute phases under strict experimental conditions.

The present report deals with the study of 6 cases of pellagra and their response to a diet low in minerals and in vitamins C, D and G.

Materials and Methods. The 6 cases chosen for this experiment were typical. Four of the patients were white males and the other 2 were negroes. All had a definite history of a low food intake, and 3 of the males and 1 of the females had a history of alcoholism.

Five of the patients had stomatitis, 4 patients had diarrhea and anal lesions and 4 had mild mental symptoms. Bilaterally symmetric dermatitis characteristic of pellagra was found on the hands of all patients. Both females had vaginal ulcerations and large butterfly-shaped, symmetric lesions of the vulva, thighs and anus, typical of pellagra. The reflexes were essentially normal in all patients.

Each patient received a daily diet of 2300 calories (carbohydrate, 1700; protein, 110; fat, 490) consisting of cornmeal mush, cornmeal muffins, pork fat, maple syrup, polished rice, cornstarch pudding, coffee and sugar. This diet was administered from the time the patient entered the hospital until the skin lesions had cleared with the exception of Case 5 (see case history). Every effort was made to induce the patients to eat the full 2300 calories. They were carefully watched and were not allowed any other nourishment.

The diet used in this experiment seems even more restricted in mineral content and in vitamins D, C and G than Goldberger's pellagra-producing diet.⁷ The present diet does not contain the following foods that are found in Goldberger's pellagra-producing diet—cabbage, collards, turnips, sweet potatoes, wheat flour and hominy grits. (He produced pellagrous lesions of the scrotum in 6 of 11 normal subjects after 6 months on his diet.) While the diet used in this experiment is restricted in vitamins D, C and G, it is not believed that all the traces of the vitamins are absent. It is noteworthy that the vitamins and protein content of this diet are less adequate for normal nutrition than Goldberger's diet.

The case histories follow in the order observed in the hospital:

CASE 1.—G. H. (No. 134043), a white male, aged 48 years, entered the hospital complaining of burning, itching and swelling of the hands of 10 days' duration.

Family history and past history were irrelevant.

Present Illness. Patient enjoyed good health until 8 months before admission. At that time he became depressed, began drinking wood alcohol, and rarely ate any food, resulting in a loss of 30 pounds in weight. Three weeks prior to admission (October 21, 1930) to the hospital he observed marked soreness and burning of the tongue and a severe diarrhea, 8 to 12 stools a day. Ten days later he developed large, symmetrical red areas over the dorsum of his hands which soon become swollen. They were pruritic and a yellowish material oozed from their surfaces. At this time he noticed vesicles over his lips and the pain in his tongue increased. He had no symptoms of dementia.

Physical Examination. Showed a somewhat undernourished white male, aged 48 years, mentally clear, lying quietly in bed. The dorsum of both hands and wrists were covered by large, symmetrical areas of reddish color. They were sharply defined from the surrounding skin. The epithelium over the lesions was tense and in areas replaced by large cracks. Small vesicles and large areas of crust formation were observed. The general physical examination was negative.

Laboratory Findings. Red blood cells, 4,900,000; hemoglobin, 75 per cent. Gastric analysis showed an absence of free hydrochloric acid after alcohol administration, but a trace was found after histamin injection.

Progress. Patient was placed on the experimental diet. The diarrhea ceased on the second day and on the fourth day his mouth and tongue were free of symptoms. Desquamation of the skin lesions was observed on the fifth day and was complete on the twelfth day. All signs and symptoms disappeared during the first 2 weeks. He gained 3 pounds in weight and was discharged on the twenty-third hospital day. He appeared well when seen 2 weeks later, despite several mild alcoholic debauches in the interval.

CASE 2.—E. F. (No. 123692), a divorced negress, aged 41 years, entered the hospital complaining of a vaginal discharge of several weeks' duration.

Family history and past history were irrelevant.

Present Illness. For several years the patient had lead a solitary life, prepared her own food and subsisted largely on oatmeal. She does not know whether or not she has lost any weight. About 6 months before admission she observed hyperpigmentation of the skin around the vagina and rectum and over the dorsum of the hands. Her condition remained about the same until 3 weeks prior to her hospital entry, when all lesions rapidly became worse and she observed a foul-smelling watery discharge from the vagina. At about this time she developed a severe diarrhea, 15 to 20 stools a day. The symptoms remained constant until her arrival at the hospital (February 13, 1931).

Physical Examination. Showed a well-developed but edematous negress, aged 41 years, lying placidly in bed. She was moderately demented. The eyelids, face, extremities and abdominal wall were edematous. The skin over the hands, wrists and adjacent portions of the arms was thickened, rough and pigmented. These lesions were bilaterally symmetrical. Her neck was similarly involved. A large symmetrically placed area involved the vulva and adjacent portions of the thighs and anus. It was pigmented, thickened and undergoing maceration. The tongue and pharyngeal walls were reddened and swollen. Mucous membranes of the mouth and vagina were bright red in color. Patient had classical physical signs of mitral stenosis associated with cardiac decompensation.

Laboratory Findings. Red blood cells, 4,300,000; hemoglobin, 75 per cent. Repeated smears from the cervix showed many inflammatory cells and almost pure infection by spirochetes. Free hydrochloric acid was absent from the gastric contents after alcohol and histamin administrations.

Progress. The skin lesions began to desquamate during the latter part of the second week on the experimental diet. This process slowly progressed and by the end of the fifth week the epithelium was thin, smooth and shiny. It still remained deeply pigmented. Mucous membranes of the mouth and vagina slowly improved and appeared normal during the fifth week. Patient remained 8 weeks on this diet. Her appetite became poor toward the latter part of the experiment, perhaps due to the vitamin C deficiency, and she ate only when urged. When seen 2 months after her discharge from the hospital she was decompensated, and the sites of the former pellagrous lesions were covered by thin, atrophic, deeply pigmented epithelium. The mouth and vagina appeared normal. The dementia was unchanged.

CASE 3.—T. S. (No. 141315), a white male, aged 44 years, entered the hospital complaining of itching of the hands of 3 weeks' duration.

Family history and past history were irrelevant.

Present Illness. During the spring of each of the past 4 years the patient had areas of itching and burning, symmetrically placed over the dorsum of the hands and wrists, followed by a dermatitis, which each time appeared only after weeks of drinking. With the onset of the skin lesions he ceased drinking, and his hands returned to normal several weeks later.

During the 8 months preceding his entrance to the hospital he drank



FIG. 1.—Showing the symmetrical lesions of pellagra.

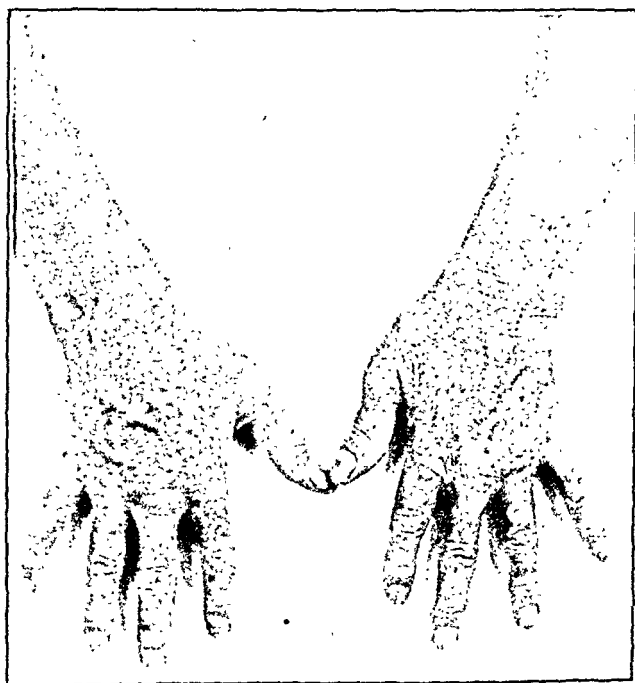


FIG. 2.—The same hands 23 days later. Note the chief residual change is due to freckles.

over 1 pint of denatured alcohol daily and rarely ate food. He lost 20 pounds in weight. Three weeks before entrance (July 7, 1931) he observed large areas of redness over the dorsum of the hands. A week later he noticed a band of similar appearance surrounding his neck. Soon afterward vesicles appeared along the neck and hands. A few days later each of the lesions became pruritic. At about this time the stools became numerous and watery in character. Several days before coming to the hospital he observed pitting edema of the ankles and numbness and burning of the hands and feet.

Physical Examination. Showed a fairly well-nourished, middle-aged man, mentally clear, lying quietly in bed. The tongue was beefy red and swollen. The pharyngeal walls and mucous membranes were reddened. Extending around his neck was an area, several centimeters in width, which consisted of large crusts surrounded by serohemorrhagic exudate. The dorsum of the hands and the adjacent portions of the arms were covered by bilaterally symmetrical lesions, characteristic of pellagra. They were raised and well demarcated from the adjoining skin and contained innumerable vesicles, crusts and areas of hemorrhage. Smaller but similar appearing symmetrical areas were observed on the dorsum of both great toes. Pitting edema of the ankles and hyperesthesia of the feet were demonstrated. The reflexes were normal.

Laboratory Findings. Red blood cells, on admission, 2,750,000; hemoglobin, 35 per cent. Red blood cells, at discharge, 3,910,000; hemoglobin, 70 per cent. Free hydrochloric acid was absent after the administration of histamin.

Progress. Patient was given the experimental diet and the lesions improved considerably during the first week. During the second week the dermatitis and the redness of the mucous membranes, tongue and pharynx disappeared. The patient lost 17 pounds while in the hospital, some of which was undoubtedly associated with the disappearance of the edema. He was discharged after 37 days on the diet. He was seen 6 days later and was in good health.

CASE 4.—R. K. (No. 135450), a white male, aged 73 years, entered the hospital complaining of painful, burning areas on the hands.

Family history and past history were irrelevant.

Present Illness. Patient had been in the habit of drinking 1 pint a day or more of wine for many months. For an unknown period of time he had had a poor appetite and lived on occasional small amounts of coffee, bread, potatoes and meat. During this time he lost 10 pounds in weight. He stated that the pruritic lesions appeared on the dorsum of the hands 6 days prior to admission (July 28, 1931). The following day these areas were observed to contain vesicles and blood oozed from some of the cracks. He had a mild coryza several days before entering the hospital. There was no history of diarrhea.

Physical Examination. Revealed a well-developed and nourished elderly man, lying quietly in bed. He had a moderate amount of dementia (it is possible cerebral sclerosis may have been the etiologic factor). The pharyngeal wall and the tip of the tongue were reddened. Over the dorsum of the lower third of both forearms and extending over the hands and fingers were symmetrical, well-demarcated lesions characteristic of pellagra. Vesicles and crusts were observed. The palpable arteries were hard and tortuous.

Laboratory Findings. Red blood cells, 3,730,000; hemoglobin, 79 per cent. Free hydrochloric acid was absent from the gastric content after administration of alcohol and histamin.

Progress. On admission the patient had an unexplained temperature of 39° C. which fell to normal within a few days. He was given the experi-

mental diet and there was rapid improvement of the skin lesions. He remained on the diet 20 days and lost 15 pounds. He was discharged improved. When seen 2 weeks later he was in good condition.

CASE 5.—A. S. (No. 135696), a married negress, aged 25 years, entered the hospital complaining of discoloration of the hands and feet, and pain in the hands, feet, mouth, rectum and vulva of more than 3 months' duration.

Family history and past history were irrelevant.

Present Illness. Patient had drunk heavily of strong liquor each day for 2 years. During the past year she ate occasional small amounts of green vegetables, fruits, cereals and meat. About 3 months before admission to the hospital (July 1, 1930) she noticed soreness of the throat, rectum, vagina and increased pain and pigmentation in her hands and feet. From that time on she lost weight constantly, and though her pains were less severe, her lesions became worse. Diarrhea and dermatitis were not present.

Physical Examination. Showed a well-developed, undernourished negress, lying comfortably in bed. The tongue, throat and mucous membranes were diffusely reddened. Symmetrical glovelike lesions extended over the hands and arms. The vagina and cervix were inflamed and there were small symmetrical areas of inflammation around the anus.

Laboratory Findings. Gastric analysis showed no free hydrochloric acid after alcohol administration but a trace of free acid was demonstrated after histamin injection.

Progress. Patient was given a high caloric diet and frequent large feedings of tomato juice and yeast. Dermatitis slowly improved. She was discharged 51 days after admission.

The patient was readmitted to the hospital 13 months later with symptoms as before.

Interval Note. For several months after her discharge the patient continued to improve but then again started to drink heavily, averaging from $\frac{1}{2}$ to 1 pint of whisky and several bottles of beer daily. Her daily diet often consisted of "a bit of vegetable, a swallow of milk or a morsel of salt pork." Lesions similar to those of the first admission developed at least 6 months prior to readmission. In addition, she had large areas of pruritus and discoloration about the vagina and elbows. For the next few months her mouth and throat became alternately sore and well. The month preceding readmission her sore throat returned, leukorrheal discharge became marked and she experienced dribbling and burning on urination. During the 2 weeks preceding admission she became worse, vomited often and lost 10 pounds in weight.

Physical Examination. Showed a well-developed, undernourished negress, aged 25 years, lying in bed. The throat, right side of the mouth, sides and tip of the tongue were injected. Large bilaterally symmetrical areas of thickened and pigmented epithelium were located over the hands, wrists, elbows, antecubital fossæ and perineal areas. The pigmented and thickened epithelium around the vagina and anus was macerated. The perineal lesion measured 16 cm. across.

Laboratory Findings. Red blood cells, 3,340,000; hemoglobin, 60 per cent. Gastric analysis on admission showed an absence of free hydrochloric acid after the administration of alcohol and histamin. Two weeks later a trace of hydrochloric acid was demonstrated following histamin injection.

Progress. Patient was placed on the experimental diet which was well tolerated for 2 weeks. During this time she gained 5 pounds in weight, and the dermatitis improved somewhat but the soreness of the mouth and throat became worse. Patient received disturbing news from her mother

and refused to eat. During the next $3\frac{1}{2}$ days she ate less than 500 calories, and her diet was changed to include anything that she might wish to eat. She then proceeded to vomit everything she ingested during the next $5\frac{1}{2}$ days. The lesions progressed rapidly and she lost 12 pounds in weight. A duodenal tube was inserted and she was fed a high caloric diet rich in vitamins and proteins. She gradually improved and the remainder of her convalescence was uneventful. She was seen 2 months later and the sites of the pellagrous lesions were covered by thin, deeply pigmented epithelium.

It is noteworthy that while the full number of calories of the experimental diet were ingested, the skin lesions improved slowly; but when the patient refused to eat the lesions rapidly became worse.

CASE 6.—C. C. (No. 142953), a Norwegian-born laborer, aged 53 years, entered the hospital because of painful lesions of the hands, neck and face of 6 weeks' duration.

Family history and past history irrelevant.

Present Illness. For the past 4 or 5 months the patient has been forced, by economic reasons, to limit his diet to bread, coffee and an occasional piece of meat. Six weeks prior to entry the patient observed symmetrical lesions of redness over the dorsum of the hands, followed soon afterward by a similar process on the neck and face. The lesions on the hands gradually involved the phalanges and lower two-thirds of the arms. He has had diarrhea and some loss of memory for an indefinite time. For several weeks he has had a mild cold. During the past year he has lost 50 pounds in weight. The patient has not imbibed any alcoholic beverages for 20 years.

Physical Examination. Showed a well-developed, emaciated white man, lying quietly in bed. Bilaterally symmetrical areas of dermatitis extended over the fingers, hands and arms. Encircling the neck and over the face and nose were large similar appearing, reddish areas with vesicle formation and crusting. The pharyngeal walls were injected. The tongue was smooth and over its right side was an area of redness, 0.5 cm. across. The remainder of the physical examination was negative.

Laboratory Findings. Red blood cells, 4,430,000; hemoglobin, 80 per cent. Gastric analysis showed no free hydrochloric acid after alcohol or histamin administration.

Progress. The patient was placed on the experimental diet and the skin lesions rapidly became better. They were replaced by thin, pink colored normal skin at the end of 12 days. The red area described on the side of the tongue slowly spread over the surface of the entire organ. It was never associated with burning or pain. The diarrhea became somewhat better. The sensorium cleared, but the weight remained constant at 101 pounds. Because of extreme emaciation and the fear of the development of another disease, he was placed on a high caloric diet at the end of 3 weeks. The tongue rapidly returned to normal and his weight gradually rose to 110 pounds. He was seen 2 months after discharge and was in good health.

Discussion. It has been shown in the experiments reported here that the skin lesions of 5 pellagrins improved strikingly on a diet low in vitamins C, D and G (pellagra-preventive factor). The other case (Case 5) in the series had partial improvement of the dermatitis, a gain of 5 pounds in weight, and a return of gastric acidity during the 3 weeks she tolerated the diet. However, during these 3 weeks on the restricted diet her stomatitis slowly became worse. She became mentally upset and refused food. The diet

was changed and tube feeding was undertaken, with recovery of the patient. It is worthy of emphasis that her lesions became worse during the 9 days that her caloric intake was so low. As soon as the skin lesions cleared several of these patients were removed from this experimental diet in order that they might not fall victim to some other diseases. Some were greatly emaciated and further experimentation might have proved dangerous. Four of the patients suffered a loss of weight. This is partially explained by the disappearance of edema in 3 cases.

In general, the skin lesions improved during the first or second hospital week and the epithelium was apparently recovered by the third week. Many of the common symptoms were relieved while the patient was on this diet, though dementia and burning of the feet did not improve.

The interpretation of the striking improvement in the dermatitis is difficult. When first seen some of these patients had temporary mild infection and in all instances the patients were given rest, thus making it difficult to say that all of the improvement was due to the diet. It is perhaps possible that these patients were on the road to recovery and continued to improve despite the restriction of diet. Their clinical histories indicate that they had eaten little prior to their admission to the hospital and in all cases the patients stated they were becoming worse when they sought relief in the hospital. While this diet is woefully deficient in many respects, it is not thought to be devoid of all traces of vitamins. Perhaps the patients received more essential elements from this restricted diet than from the paucity of food they ingested before coming to the hospital. The observations that Case 5 rapidly became worse when she refused the diet is suggestive that this diet is certainly more beneficial than the absence of food. Of course, the question as to the degree of depletion of the various substances in the bodies of these patients at the time they came to the hospital must remain unanswered. It seems logical that if pellagra is caused by specific depletion of some factor, this factor would be low at the time of the disease.

It is impossible to know whether or not the skin lesions would have recurred had the patient continued indefinitely on this diet. At the present time it seems logical to think of a secondary factor in the development of pellagra. For example, we observed a case who developed pellagra in her home despite the fact that she ate generously of the usual household foods and did not take alcoholic beverages. When first seen in the hospital this patient was regarded as being an unusually severe case and was not placed on the experimental diet. She died 5 days after admission to the hospital despite the fact that she was getting a generous diet high in proteins and the known vitamins. The postmortem examination

revealed no adequate cause for her death. In view of Castle's⁸ recent work, it seems that there may be an underlying gastric disorder. This theory is supported by the observation that a fairly high percentage of the cases have achlorhydria which usually disappears several months after recovery from the disease. On the other hand, I have demonstrated⁹ that ventriculin, which is curative for pernicious anemia, protects and cures the pellagra-like condition described in rats. This observation suggests some etiological relationship between vitamin G deficiency and the development of pernicious anemia.

The diet given the pellagrins in this experiment has been demonstrated to be inadequate for the proper nutrition of young rats.⁹ When limited to this diet the rats lost weight, developed alopecia and dermatitis and subsequently died. This fact plus the theoretical dangers of giving a restricted nonpalatable diet to diseased patients make us realize that it should be used with the greatest of care. Although this diet may not be a cure for pellagra, yet these people have improved in spite of it, suggesting that rigidly controlled observations are necessary for further study of this disease.

Summary and Conclusions. 1. It has been shown in the cases reported here that the skin lesions of 5 pellagrins improved strikingly while receiving a diet believed to be lower in protein content and in vitamins C, D and G than so-called pellagra-producing diets.

2. The possibility of a secondary factor in the production of pellagra, perhaps analogous to the gastric defect of pernicious anemia, is thus suggested.

3. The indiscriminate continuous administration of such a restricted diet to pellagrins is not recommended.

REFERENCES.

1. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Further Studies of the Thompson-McFadden Pellagra Commission: A Summary of the Second Progress Report, *J. Am. Med. Assn.*, 1914, **63**, 1090.
2. Wood, E. J.: Pellagra, *Oxford Med.*, 1928, **4**, 307.
3. Funk, C.: *Die Vitamine*, Wiesbaden, 1914.
4. Goldberger, J.: The Transmissibility of Pellagra, *U. S. Pub. Health Rep.*, 1916, p. 3159.
5. Goldberger, J., Waring, C. H., and Willets, D. G.: The Prevention of Pellagra, *U. S. Pub. Health Rep.*, 1915, **30**, 3116.
6. Goldberger, J., Wheeler, G. E., and Sydenstricker, E.: The Relation of Diet to Pellagra Incidence, *U. S. Public Health Rep.*, 1920, **35**, 648.
7. Goldberger, J., and Wheeler, G. A.: Experimental Production of Pellagra in Human Beings by Means of Diet, Hygienic Laboratory, Washington, *Bull.* 120, February 7, 1920.
8. Castle, W. B., Townsend, W. C., and Heath, C. W.: Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia; Nature of Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to Effect of Liver Feeding, *Am. J. Med. Sci.*, 1930, **180**, 305.
9. Spies, T. D.: Response of Rats to So-called "Pellagra-producing" Diet. (To be published.)

ABSORPTION FROM THE PLEURAL CAVITY OF DOGS.

II. THE LYMPHATIC SYSTEM.*

By WILLIS S. LEMON, M.B.,

HEAD OF SECTION IN DIVISION OF MEDICINE, THE MAYO CLINIC; ASSOCIATE PROFESSOR
OF MEDICINE, THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,

AND

GEORGE M. HIGGINS, PH.D.,

ASSOCIATE IN DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY, INSTITUTE OF
EXPERIMENTAL MEDICINE; ASSOCIATE PROFESSOR OF EXPERIMENTAL BIOLOGY,
THE MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH,
ROCHESTER, MINN.

In former communications, the absorptive mechanism from the peritoneal cavity of dogs was described.^{2,4} Other studies made on the mechanism of absorption of particulate material from the pleural cavity of dogs have already been published.³ Part I, the cytologic aspect; Part II, the present study, describes the lymphatic channels of the thorax which appear chiefly responsible for the removal of such particulate matter. The description will be confined to those lymph nodes and vessels that are readily seen by natural methods of filling.

Method of Experiment. A finely divided particulate graphite preparation was injected directly into the pleural space, usually in the ninth interspace. To avoid the parenchyma of the lung manometric readings were first taken, to be sure that the needle was in the pleural cavity, but not in contact with tissue of the lung. The manometer was then detached and a sterile graphite suspension was injected. Ordinarily 5 to 15 cc. was used, the exact amount depending on the weight of the dog. The animals were killed and carefully dissected at intervals following the injection ranging from 1 hour to 4 months. Most of the animals were fed a heavy fat meal approximately 3 hours preceding necropsy to facilitate identification of the cisterna chyli, thoracic duct and related lymph vessels.

Observations. When animals were examined within an hour after the injection of the graphite suspension into the right pleural space, two characteristic observations invariably followed. (1) The injected material acted as an irritant on all the structures within the thorax, causing edema and hyperemia, so that the pleural surfaces were inflamed and edematous and the bloodvessels stood out prominently; (2) the mediastinum was not an impermeable barrier between the two sides of the thorax; in every instance approximately equal amounts of serous effusion were present in both sides of the thorax, regardless of the side into which the graphite had been injected; (3) the inflammatory reaction seemed to grow in intensity up to the eighteenth or twentieth hour; but it

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gradually receded and usually all effusion was absorbed by the fourth or fifth day.

The pleural fluid, as has been described,⁴ had certain constant characteristics. It was made up of serum blackened by graphite and contained erythrocytes and leukocytes, as well as phagocytes of the mononuclear variety. In the early experiments, some of the graphite was free within the fluid, but as time progressed and inflammation receded, the amount became reduced until all was included within phagocytes. The earliest phagocytic reaction was demonstrated by the polymorphonuclear leukocytes. Later, there was a gradual increase in the number of nongranular mononuclear phagocytes which we have described as clasmotocytes.

Certain differences in behavior of the serous membranes were uniformly observed. It was significant that the visceral pleura took but small part in the inflammatory reaction. It was never as edematous or hyperemic as the parietal pleura, and although the visceral pleura was literally bathed in black fluid for a period of 4 or 5 days, yet the lymphatic channels of the visceral pleura were never seen and the lymph nodes at the hilum took a lesser part in the absorption than those in other areas, especially the sternal and the tracheal lymph nodes. Nodes of the hilum in this contribution include the bronchopulmonary nodes together with the superior and inferior tracheobronchial group. The gross and the microscopic examination of the lung failed to reveal any evidence that the injected material had passed through the visceral pleura or that the lung contained any of the graphite.

The reaction of the diaphragmatic pleura was essentially similar to that of the pleura covering the lungs. Areas of black coagulum were present here and there, but these were merely adherent and could be brushed off easily. In small isolated areas, however, the granules of graphite were contained in phagocytes that apparently had penetrated the pleural surface and were packed within the serous membrane. There was no instance in which the diaphragmatic lymph vessels were filled nor did lymph spaces between the muscle fibers contain graphite in any form. It was evident that the diaphragm is not an efficient drainage mechanism for the pleural space. The contrast between this and the behavior of the diaphragm with relation to drainage from the peritoneal space was striking.²

In contrast to this sluggish or negative reaction of the diaphragmatic and visceral layers of the pleura and the apparent lack of drainage from the pleural cavity through the lymph channels of the lung, the mediastinum and all its subdivisions as well as the regional lymph nodes related to it assumed the most remarkable signs of activity. In every instance, even in experiments lasting but 1 hour, the mediastinum became densely colored and the anterior mediastinum hung like a black curtain between the two sides of the thorax. There was a peculiar adhesive quality about the mediastinum that

seemed to attract the irritating material to itself. Almost invariably the mediastinum was not only thickened but formations of large exudative masses were attached to it; these were firmly adherent to both sides of the mediastinum as well as to the pulmonary ligaments. When examined in the early stages they consisted largely of graphite-laden polymorphonuclear leukocytes, comparable to those appearing in the effusion. In the earlier observations free graphite was identified among the mesothelial cells of the mediastinum; erythrocytes were numerous, and evidence of phagocytosis was observed in the polymorphonuclear leukocytes as well as in the nongranular mononuclear phagocytes. In later stages changes in the mediastinal tissue occurred much as in the parietal pleura. The cellular inflammatory reactions such as hyperemia and edema gradually disappeared and subsequent organization of the tissue occurred gradually. Capillary invasion took place, fibroblasts appeared in larger numbers with the result that new connective tissue invaded these exudative masses. The fibroblasts themselves were similar to those usually seen in the early constructive processes terminating in the formation of fibrous tissue. The phagocytic nongranular mononuclear cells appeared to change from round to elongated cells resembling fibroblasts. These retained the ingested graphite and it served to distinguish them from fibroblasts which appeared to lack the function of phagocytosis.

Regardless of the time the animal was permitted to live, the mediastinum remained black throughout life. In all of the experiments and in the many observations and dissections that were made, there was no evidence to show that actual lymphatic vessels were present in the anterior mediastinum or that the anterior mediastinum assisted in the transference of fluid and particulate matter from the pleural space. There are many suggestive facts, however, which would lead to that conclusion and further work is being done in the hope that the rôle of the mediastinum as a transferring mechanism can be established. It seems probable that it occupies the same place in pleural absorption that the omentum does in peritoneal absorption.¹ There is no question but that the mediastinum is a protective mechanism, absorbing large quantities of any irritating material which may be present, retaining it as though it were included in a sponge and finally fixing it within itself by the production of connective tissue.

In no single experiment were all of the lymphatic tracts completely delineated, and the description that will follow is a composite of all of the observations made in the separate experiments. A standard description is given, however, showing observations commonly encountered in an experiment of short duration.

Typical Experiment. An animal was fed 75 cc. of butter and cream, stained with Sudan III, at 8.15 A.M. Sixteen cubic centimeters of graphite suspension was immediately injected into the right side of the thorax and

necropsy was done at 11.15 A.M., exactly 3 hours after the beginning of the experiment. When the abdomen was opened the cisterna chyli was distended with pink lymph and the lymphatic radicles of the mesentery were deep pink. The thoracic duct itself contained pink lymph and it could be traced to the lymphatic venous confluence. Lymphatics were not visible on the pleural surface of the diaphragm. This constant negative observation lends assurance to the belief that the diaphragmatic lymphatic system has to do only with the removal of peritoneal exudates. Examination of the lymph nodes revealed that the retroperitoneal node, dorsal to each kidney, was densely black and the lymphatic tracts leading backward from the posterior wall of the thorax was readily seen passing beneath the lumbar attachment of the diaphragm into the retroperitoneal space, and leading directly to this node. Exceedingly small lymph vessels passed from the node into the cisterna chyli. A similar picture occurred on both the right and left sides. The nodes in relation to the spleen were also slightly dark, although there was a question whether this was actually due to pigment. It has been shown that in a certain percentage of dogs lymph vessels pass from the diaphragmatic pleura posteriorly over the surface of the cardia to a lymph node in the hilum of the spleen. This is the only suggestion we have that the diaphragmatic pleura may have absorbed particulate material. No other lymphatic nodes in the abdomen were black. On opening the thorax, one is impressed by the fact that the dog has literally a single thoracic space and that generalized inflammation occurs rapidly after the insertion of an irritant into the pleural cavity. Thirty cubic centimeters of a black serous effusion was removed from the right side and approximately an equal amount was taken from the left side. Smears made of the fluid contained many erythrocytes and leukocytes. Some free graphite was found and the polymorphonuclear cells had already phagocytosed many granules of pigment. There were relatively few monocytes, but they also contained large quantities of pigment, packed into large granules. The visceral pleura was entirely free of any evidence of inflammation and, although both lungs were bathed in this black serous effusion, there was no evidence that the visceral pleura had absorbed pigment. Even the nodes of the hilum of the lung were not abnormally dark. The conclusion was clear that the lymphatics of the lung and visceral pleura have little, if anything, to do with the removal of such particulate material from the pleural space. The conclusion was also apparent that the material was picked up by the cells of the costal pleura, and the cells of the mediastinal pleura as well as by the pulmonary and the pericardial ligaments. There seems to be no other explanation than that the pigment passed into these mesothelial structures and then entered their related lymphatic vessels and passed into the lymph nodes in the anterior and posterior mediastinum.

On both sides the backward flow of lymph into the retroperitoneal space, dorsal to the kidneys, could be seen definitely. These lymph channels arose in the dorsal costal pleura about the level of the tenth rib; on both sides, the forward lymph flow started in the interval between the ninth and tenth ribs. On the left side a single lymph vessel passed forward parallel to the sympathetic nerve trunk as far as the level of the third rib, where it divided into two, one of which passed over the thoracic duct and the esophagus and entered a large and elongated densely black lymphatic node along the esophagus. The larger branch continued forward, crossed the sympathetic nerve trunk and divided into three branches, two of which passed into the upper pole of the same lymph node, and the third, forward over the dorsal anterior wall of the thorax. The upper of the two branches entering the node divided into two, the superior of which proceeded forward to enter into a second smaller lymph node. The efferent vessels from the

nodes were joined in their course toward the entrance into the thoracic duct by afferent vessels from the sternal nodes which ran parallel to the internal thoracic artery. The intercostal segmental lymph vessels entering this longitudinal tract were not encountered in this experiment.

On the right side of the thorax the pattern made by the forward-flowing lymph vessels was more intricate than on the left. Only 2 vertebral lymph nodes were present, 1 in the eighth and 1 in the fourth interspace, and both lateral to the azygos vein, between it and the sympathetic trunk. A long collecting lymph vessel received the segmental lymph vessels from the interspaces as tributaries, thus uniting these 2 nodes. Vessels from the third and fourth interspaces also were afferent to the upper of the 2 vertebral nodes from which efferent vessels formed a plexus on the surface of the trachea. (Fig. 1.) Their course upward was interrupted by several small tracheal lymph nodes. Finally the plexus united in 2 larger tracheal nodes lying opposite the head of the first rib. Lymph tracts from these nodes communicated with tracheal nodes on the opposite side; others united with the lymph vessels, passing upward through the mediastinum parallel to the internal thoracic artery and then proceeded to the venous confluence on the right.

The backward course of the lymphatics posterior to the ninth rib into the retroperitoneal space was readily made out. (Figs. 2, 3 and 4.) There was no question about the existence of these lymph vessels; they could be seen just as well as veins or arteries and could be traced throughout their course to the point at which they joined the superior pole of the lymph node. From this node the connection with the cisterna chyli was easily seen. By using a colored medium and injecting directly into the node, the cisterna as well as the thoracic duct was completely filled and the venous confluence was identified. By the same method, however, the afferent vessels to this node were not injected, since the strength of their valves protected against a reverse flow and the vessels ruptured before the valves were overcome.

The sternal lymph nodes were densely black and the anterior mediastinum hung as a black curtain between the pleural spaces. Festoons of black exudative material hung from this central partition. Efferent channels from the sternal lymph nodes passed onward parallel to the internal thoracic bloodvessels toward the lymphatic venous confluences. On the left side they united either directly with the thoracic duct or indirectly after union with efferent vessels from the tracheal lymph nodes and on the right they combined with efferent vessels from the tracheal lymph nodes and passed to the right cervical lymphatic confluence.

Lymph Nodes of the Thorax of the Dog. On the basis of our study, the lymph nodes of the thorax in the dog may be divided into parietal lymph nodes associated with the drainage of the thoracic wall, and visceral lymph nodes associated with drainage of the thoracic viscera.

Parietal Lymph Nodes. These nodes fall into 3 groups, the sternal, the vertebral and the diaphragmatic.

A certain latitude of variability may always be assumed in describing any portion of the lymphatic system; this same observation holds true concerning the sternal nodes. In all the animals we have examined there were 1 or 2 sternal lymph nodes on each side, immediately anterior to the border of the triangularis muscle at the level of the first rib. In some animals, however, this simple arrangement was replaced by a chain of 2 or 3 lymph nodes, close to the sternum and approximately at the level of

the first and second ribs. They were in all instances closely approximated to the internal thoracic bloodvessels.

The vertebral nodes were very small and extremely variable in their arrangement. As a rule, these nodes were not identified; at other times, 1 or 2 very small nodes were found just lateral to the sympathetic trunk and usually in the interspaces between the heads of the ribs. Segmental nodes were not identified in each interspace, although when present they received the drainage from the segmental intercostal lymph vessels. There was, however, a rather more segmental distribution on the right side, and it was not uncommon to find a node of varying size either above or below the entrance of the azygos vein into the vena cava. In some animals 2 nodes were present at this site, 1 above and 1 below the confluence of the azygos vein and vena cava. Occasionally very small lymph nodes were found lateral to the azygos vein in one or more of the interspaces as low as the eighth, but such segmental nodes were never seen below the eighth interspace.

In most of the animals studied lymph nodes were not seen on the pleural surface of the diaphragm. In others a group of very small nodes was identified at the insertion of the phrenic nerve into the diaphragm. Evidently they are less well developed in the dog than in primates. Scott and Beattie described 2 or 3 small nodes lying on the central tendon of the diaphragm and usually surrounding the inferior vena cava. They found these nodes constant in apes and in larger old-world monkeys, but frequently absent in smaller monkeys. In South American monkeys they are variable or absent in the smaller members of the group.

Visceral Lymph Nodes. The visceral nodes may be divided into 4 groups: mediastinal, pulmonary, tracheobronchial and tracheal. We shall not describe the pulmonary lymph nodes because they appear to play a small part in the removal of particulate matter or fluids from the pleural space. Scott and Beattie distinguished between the mediastinal and the tracheobronchial nodes, and remarked that it was common in pathologic literature to confuse these nodes. They felt that the nodes are often called mediastinal when they should be called tracheobronchial: "The 2 groups are distinct and can be readily differentiated by the fact that the tracheobronchial group is always pigmented with carbon particles in animals living in city atmosphere while the mediastinal glands remain clean."

The mediastinal nodes comprise 3 or 4 small nodules which lie either ventral to the superior vena cava, or between the veins and the trachea. Usually they are very small and in our experience were not at all constant. The tracheobronchial nodes (Fig. 5) were in the superior and inferior angles formed by the division of the trachea and were fairly large. In our observations the tracheal nodes were variable in number and in position. There were 3 or 4, however, on the right side, that were fairly large and quite constant in position. One was cephalad to the confluence of the azygos vein with the vena cava, another was at the origin of the vena cava at the point of confluence of the large innominate veins and a third was lateral to the jugular vein in the first interspace. To the right of the vena cava the right surface of the trachea was visible, and on it there was frequently a group of small lymph nodes.

On the left side the arrangement of the nodes was similar but they were invariably smaller. A communication of the two sides between the 2 tracheal groups was observed by way of small lymphatic channels. The most common arrangement on the left side consisted of 1 node immediately above the arch of the aorta and 1 above and 1 below the origin of the internal thoracic artery.

Lymphatic Vessels of the Thorax of the Dog. These may be conveniently divided into two systems draining the right and the left sides. On both sides, the subdivision may further be carried into dorsal and ventral. The dorsal division may again be divided into an upper and lower subdivision.

When the graphite was introduced into the thoracic cavity, it soon became adherent to the parietal or costal pleura and usually was indefinitely distributed beneath the pleural surface. The pleura had a smoky appearance, and although the distribution was indefinite, yet in the main the discoloration occurred in parallel lines above and below the margin of the ribs. This characteristic distribution was present throughout the extent of both the dorsal and the ventral portions of the costal pleura.

Dorsal Distribution. Dorsally the distribution of the upper lymphatic vessels had a fairly characteristic pattern, but had certain distinct differences on the two sides. On the right from the eighth interspace to the fourth interspace the segmental lymphatic radicles passed into a collecting vessel which continued forward to the lymph nodes that have been described in relation to the azygos vein. (Fig. 1.) Then afferent channels passed upward, forming a plexus over the right ventral surface of the trachea to the upper tracheal nodes when the drainage continued to the right venous confluence. The efferent vessels from the tracheal nodes were joined by efferent tracts from the sternal lymph nodes and entered the cervical lymph duct at its jugular confluence. The usual drainage encountered above the third interspace formed a pattern which was less segmental. The collecting radicles passed forward and entered directly into 1 of the 2 upper tracheal lymph nodes. In only 1 instance, however, the radicles from this region coursed downward to join with the collecting trunk, that had passed forward from the eighth interspace; usually the flow in the vessels of the upper interspaces was upward to the two upper tracheal lymph nodes.

The arrangement of the collecting vessels at the upper division of the dorsal costal pleura on the left side was less complicated and usually consisted of a single vessel arising in the eighth or ninth interspace. This unpaired lymph vessel passed forward lateral to the sympathetic trunk until it reached the level of the third rib, when it inclined toward the median line, crossed to the esophagus and broke up into a plexus of varying patterns. It finally entered the lymph nodes on the esophagus previously described and then coursed forward and to the left, to join the efferent vessels from the sternal nodes. The lymph drainage from the sternum, mediastinum and costal pleura united with the thoracic duct just before it reached its confluence with the vein. With one exception, segmental intercostal branches never entered the thoracic duct. This description is somewhat different from that of Scott and Beattie, but their work was done on primates including the chimpanzee and the monkey (*Macacus rhesus*).

The drainage system of the lower dorsal costal pleura on both sides was formed by a number of small vessels which coursed downward, receiving lymphatic radicles from the tenth, eleventh and twelfth interspaces. (Fig. 2.) These were usually arranged in groups of 3 or 4 vessels which passed dorsal to the pars lumbalis of the diaphragm to a lymph node in the retroperitoneal space just above the upper pole of the kidney. This node, in turn, was connected by lymphatic vessels to the cisterna chyli.

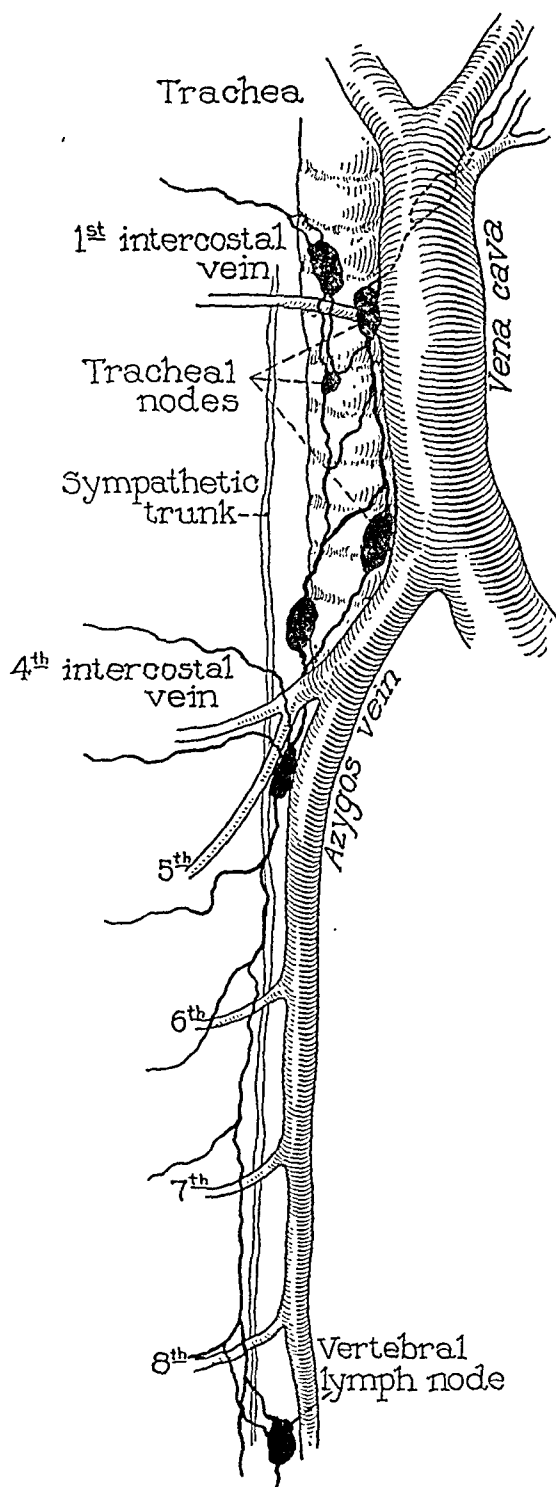


FIG. 1.—Distribution of lymph nodes and segmental lymphatics, the collecting lymphatic vessel and the lymph nodes and plexus of lymphatics in relation to the trachea.

If the diaphragm on the right side was stripped of its attachment and the liver and the kidney were retracted to the left, as in Fig. 2, the vessels could be traced in their entire course from the lower interspaces backward to the retroperitoneal space to the lymph node and then to the cisterna chyli. In a few instances this plexus from the thorax emptied directly into the cisterna before it passed through the node, but this arrangement was unusual. (Fig. 2.)

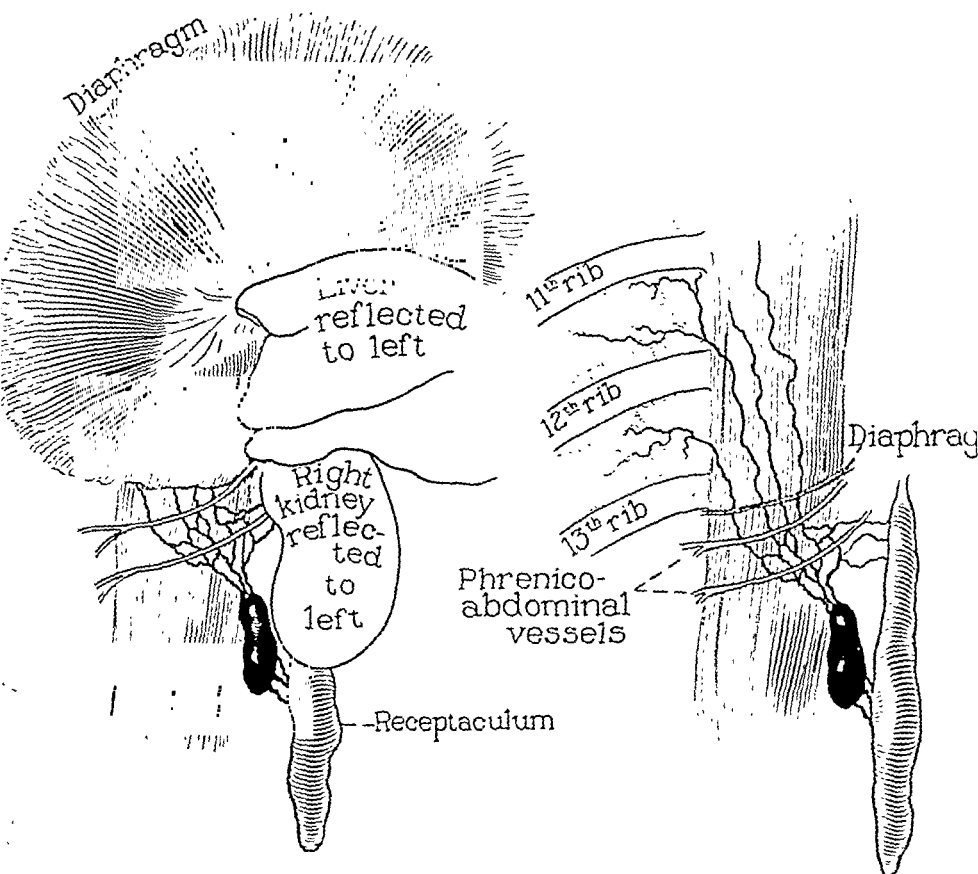


FIG. 2.—The backward course of the lymphatics, posterior to the ninth rib into the retroperitoneal space. The vessels unite in a plexus before they enter the retroperitoneal lymph node dorsal to the kidney. From it efferent vessels enter the cisterna chyli.

Ventral Distribution. Ventrally, small lymph vessels were disclosed beneath the transverse thoracic muscles close to the juncture of the ribs with the costal cartilages. These were followed distally along the anterior and posterior margins of the ribs and appear to have the same distribution as the indefinite infiltration, described for the pleura. These channels acted as collecting vessels for each interspace. They passed mesially and anteriorly somewhat parallel to the ribs, usually with a single vessel both above and below the margins of the rib, and finally beneath the transverse thoracic muscle they united to form an intricate lymphatic plexus. (Fig. 6.) The plexus was always lateral to the internal thoracic bloodvessels. It was

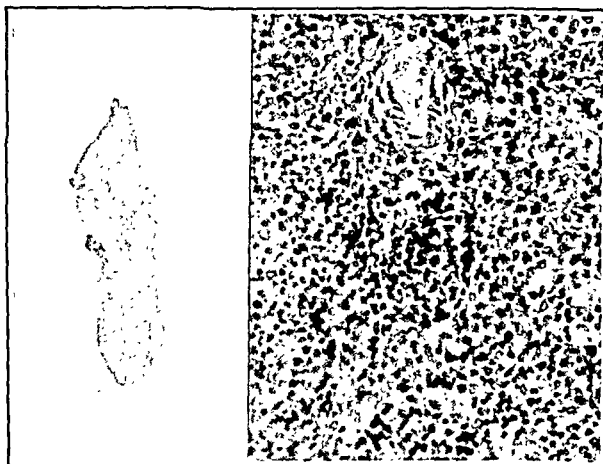


FIG. 3.—Gland dorsal to kidneys. The white gland was removed the day previous to intrapleural injection of particulate matter; absence of any pigment is shown. ($\times 200$.)

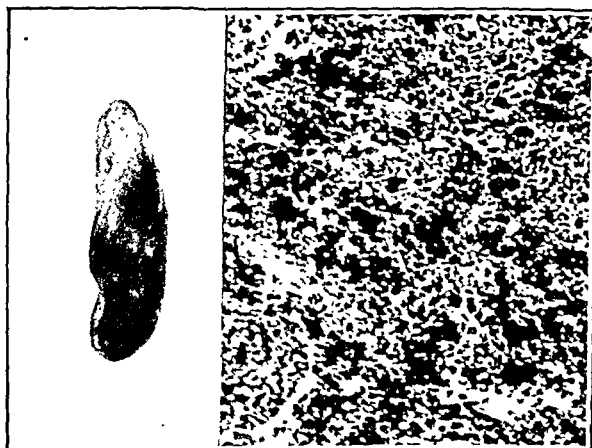


FIG. 4.—Gland dorsal to kidneys. The black gland was removed 12 hours after intrapleural injection of graphite suspension. The black gland shows the presence of large amount of pigment.

Fig. 5.
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not connected with the lymphatic plexus which carried absorbed materials from the peritoneal cavity, but was a distinct plexus and was employed only in the drainage of the ventral parietal pleura. These collecting vessels, comprising the sternal plexus, passed into the sternal lymph node which was situated anterior to the internal thoracic bloodvessels, approximately opposite the third costal cartilages. Anterior to this rib the lymphatics of the interspaces and of the pleura covering the operculum emptied into the anterior of the 2 sternal lymph nodes opposite to or above the first rib. On the right side this arrangement was usually more easily seen and the vessels were larger than those on the left side. The plexus, too, was always more complicated.

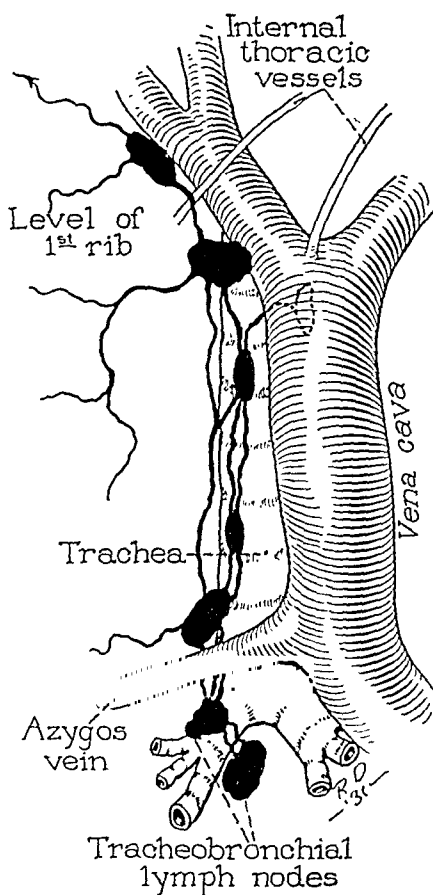


FIG. 5.—The position of the superior and inferior tracheobronchial lymph nodes and their relationship to the drainage system of the upper portion of the posterior costal pleura of the right side.

Microscopic Appearance of the Liver, Spleen and Lymph Nodes. In the pleural effusions that formed following an injection, free particulate matter was always present if only short periods elapsed between injection and exploration. This was true in experiments of five hours' duration, and in 1 experiment of 18 hours' duration. The sternal and the tracheal lymph nodes were always densely black within 1 hour. The retroperitoneal node, in relation to the kidney, became black usually within the second hour. It was obvious, then, that the lymph drainage occurred promptly and that free particulate matter was distributed into the lymph nodes together with that contained within the phagocytic cells both of the polymorphonuclear and the monocytic types. Furthermore, it appeared that the material

absorbed and transferred through the lymphatics reached the thoracic duct or the right lymphatic duct and emptied into the venous circulation within a period of approximately 1 hour; it thus became possible for such particulate material to reach the systemic circulation and to appear in the liver, spleen and bone marrow within a relatively short time after injection. On examination, grossly, of a large number of livers and spleens, there was no evidence of discoloration from pigment. On microscopic section, however, two characteristic reactions were manifest. In those examined

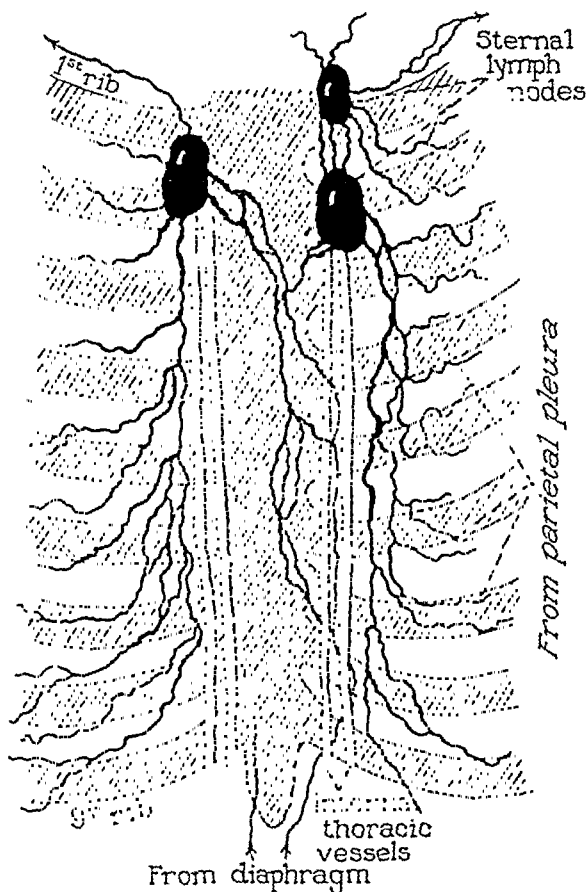


FIG. 6.—The lymphatic drainage system of the anterior costal pleura. It consists of segmental vessels uniting in a complicated plexus of vessels beneath the transverse thoracic muscles. The plexus is lateral to the internal thoracic vessels and independent of the plexus of lymphatics concerned with the drainage of the peritoneal cavity. The intermingling of the lymph from the two drainage systems takes place in the sternal nodes.

within 2 to 3 hours of the injection, the Kupffer cells were swollen to several times their original size, and they encroached on the lumen of the sinusoids, or desquamated into the lumen. This appearance always preceded the recognition of particulate matter within them. It would appear that the irritating action of the intrapleural injection was manifest following absorption and that irritation was induced within the liver preparatory to the phagocytic activity by the Kupffer cells. Particulate

matter, however, was never encountered free in the hepatic sinusoids. It was evident that the liver contained a larger amount of the absorbed material than did the spleen. Here again, however, when present it was contained within the reticular cells of the splenic sinusoids. The blood spaces did not contain free pigment and phagocytic cells containing pigment free within the sinusoids were not encountered.

In the sternal and the tracheal nodes, or in any of the nodes in the path of drainage from the thorax, a similar picture was invariably seen. If the experiment had lasted more than 2 or 3 hours the picture varied somewhat, but generally the graphite was distributed throughout the entire node. Often the lymph follicles, immediately beneath the capsule, contained graphite which was always included within large nongranular mononuclear phagocytic cells. Occasionally graphite was seen free in the lymph sinusoids or often in large mononuclear cells which had either entered the node from the draining lymph channels or had desquamated from the reticular syncytium. The dense blackening of the lymph node was due to the marked phagocytic activity of the littoral cells lining the lymphoid sinusoids. They were often literally packed with free graphite material. There was no evidence of circulating granules or of phagocytosis among the cells of the blood stream within the lymph nodes, and thus it seemed obvious that the distribution within the nodes was truly drainage through the lymphatic system.

Summary. Experiments, in which a graphite preparation was injected into the pleural space of dogs, produced an inflammation and delineation of lymphatic vessels solely by the natural method of absorption and drainage. This provides a means for the study of the functional lymphatic system of the dog's thorax and therefore includes the lymph nodes and the afferent and efferent lymph vessels in their normal position and usual distribution.

The lymph nodes in the thorax of the dog arrange themselves naturally into two main groups: parietal and visceral. The parietal group comprises the sternal, the vertebral and the diaphragmatic nodes; the visceral group includes the mediastinal, pulmonary, tracheobronchial and tracheal nodes.

Of the parietal lymph nodes, those of the sternal group, which lie at the level of the first and second interspace and receive the lymph drainage from the peritoneum, as well as from portions of the costal pleura, are the most constant in number, size, and position. The vertebral nodes are fairly inconstant in dogs. When present they lie on the intercostal muscles beneath the costal pleura just lateral to the thoracic sympathetic nerve chain. We have never identified a completely segmental distribution of vertebral lymph nodes in dogs. They are usually more commonly found on the right side than on the left. Diaphragmatic nodes are perhaps more rarely encountered than vertebral nodes. When present they lie on the tendon or near the insertion of the phrenic nerve into the muscle.

Of the visceral group of lymph nodes the mediastinal are perhaps the most inconstant. They comprise a group of three or four small nodes which lie ordinarily between the vena cava and the trachea. The lymph nodes of the tracheobronchial group are invariably

constant in size and usually in number. They lie in the superior and inferior angle of the tracheal bifurcation. The extent and distribution of the tracheal nodes are exceedingly variable. They vary in number from three to six and lie along the trachea from the junction of the azygos vein and vena cava to the level of the first interspace.

The lymph drainage associated with these nodes may be grouped into six routes, two of which conduct lymph caudad and four cephalad. The line of cleavage, so called because it represents the level on the dorsal wall of the thorax from which lymph flows cephalad and caudad, is at the level of the eighth or ninth interspace. From this level, on both right and left sides, lymph vessels pass caudad, and empty into a large lymph node which lies dorsal to the anterior pole of each kidney. Efferent vessels from these nodes lead directly into the cisterna chyli. The cephalad lymph drainage from this cleavage plane along the dorsal median line is less easily demonstrated than the caudad one. Intercostal segmental collateral vessels are not constant, although far more nearly so on the right than on the left side. On the right the collecting channels empty into the caudad tracheal group of nodes; on the left, into the mediastinal group of nodes.

On each side of the sternum the lymphatic drainage system from the ventral pleura comprises a series of segmental channels which converge to form an extensive plexus lateral to the internal thoracic bloodvessels beneath the transverse thoracic muscle. This plexus is lateral to the one which carries lymph from the diaphragm to the sternal nodes. Both pleural and abdominal lymph draining the plexus, empty into the sternal group of nodes at the level of the first and second interspaces. In the course of the lymphatic vessels through both the anterior and the posterior mediastinum communicating lymph channels permit the interchange of lymph from the two sides of the thorax. The terminal efferent vessels from the sternal and the tracheal nodes usually become confluent and together join the thoracic duct or the right lymphatic duct proximal to the lymphatic venous confluence.

BIBLIOGRAPHY.

1. Brodsky, J. F.: *Physiologie und Pathologie der Resorption aus der Pleurahöhle: I. Mitteilung: Ueber Resorption der krystallinen Stoffe unter normalen Bedingungen*, Ztschr. f. d. ges. exper. Med., 1928, **61**, 24.
2. Higgins, G. M., and Graham, A. S.: *The Lymphatic Drainage From the Peritoneal Cavity in the Dog*, Arch. Surg., 1929, **19**, 453.
3. Higgins, G. M., and Lemon, W. S.: *Absorption From the Pleural Cavity of Dogs: I. The Cytologic Aspect*, Am. J. Med. Sci., 1931, **181**, 697.
4. Lemon, W. S., and Higgins, G. M.: *Lymphatic Absorption of Particulate Matter Through the Normal and the Paralyzed Diaphragm: An Experimental Study*, Am. J. Med. Sci., 1929, **178**, 536.
5. Scott, H. H., and Beattie, J.: *The Distribution of Tuberculous Lesions in Man and Other Primates With an Account of the Lymphatic Glands and Vessels of the Thorax and Upper Abdomen*, J. Path. and Bact., 1928, **31**, 49.

REVIEWS.

A TEXT-BOOK OF PATHOLOGY. By WILLIAM BOYD, M.D., M.R.C.P. (Ed.), F.R.C.P. (Lond.), Dipl. Psych., F.R.C.S., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 946; 287 engravings and a colored plate. Philadelphia: Lea & Febiger, 1932. Price, \$10.00.

THIS book is avowedly a textbook for undergraduate and postgraduate students, not a reference book for professional pathologists, and the author has intended to limit himself to treating of the fundamentals. Notwithstanding this avowal, many of the very newest notions are discussed, especially those which seem to the author to add to our knowledge of functional pathology. His stress on the functional aspects and his short résumés of clinical symptoms aid the student in correlating the various preclinical branches of medicine with each other and in correlating the pathological with the clinical aspects of disease. In doing this the author in no way detracts interest from the morphological details. He says, "morbid anatomy is not dead and never has been, except in the hands of those whose dull minds would take the breath of life from the most vital subject," and the present volume bears witness to the truth of that statement because the author's vivid imaginative style of writing gives color and emphasis of details, and his personal enthusiasm for his subject must prove infectious to many a listless student. In fact, this book is felt to be a very emphatic and personal expression.

The Reviewer does not agree with some of the author's convictions about certain perplexing points in the etiology and pathogenesis of various conditions, or with his apparent reliance on certain recent experiments, or with some of his philosophical persuasions; but these personal points of view are always interesting and may be differentiated from the statement of proved facts. The author may seem too dogmatic on points that some would consider debatable, but as the book is intended for students he doubtless prefers to run the risk of erring in this respect, rather than to confuse the student with hair-splitting of minor details, between which the more experienced reader should be able to discriminate.

The sections devoted to special pathology (about two-thirds of the book) are much less detailed than the author's treatment of the same subjects in his "Pathology of Internal Diseases." The illustrations are largely photomicrographs, many being the same as in the other work, are well selected and technically excellent. More references are to British literature than is usual in American textbooks. I. Z.

DIABETES IN CHILDHOOD AND ADOLESCENCE. By PRISCILLA WHITE, M.D., Physician at the New England Deaconess Hospital, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. Pp. 236; 25 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1932. Price, \$3.75.

THE story of the diabetic child is one of the bright pages of modern medicine. In the pre-insulin era the life expectancy of the diabetic child

was 2 years at most. With insulin, 76 children in Dr. Joslin's series have lived 10 years or more. Furthermore, the experience with the diabetes of childhood is helping to solve some of the important problems of the disease in adults, notably arteriosclerosis. Dr. White, who has been in contact with Dr. Joslin's Clinic since before the introduction of insulin, has presented in a clear and interesting manner all the details of the management of the youthful diabetic through childhood and adolescence into adult years. She has adduced convincing evidence on the hereditary factor in the disease. The book is a worthy addition to the others which have come from the Joslin Clinic and it should be in the hands of every practitioner of medicine.

R. K.

INFECTIONS OF THE KIDNEY. By MEREDITH F. CAMPBELL, M.D., F.A.C.S., Attending Urologist, Babies Hospital, New York Nursery and Child's Hospital; Assistant Visiting Urologic Surgeon, Bellevue Hospital, New York. Pp. 343; 40 illustrations. New York: Harper & Bros., 1931. Price, \$3.00.

THIS is another of Harper's Medical Monographs, a series of convenient pocket-size works for practitioners. The present volume is quite up to the high standard of excellence set by the volumes which have so far appeared. Not intended as a reference book, the material has been presented concisely, without bibliography and with the practical interest of the reader constantly in view. The chapters on anatomy and physiology, on methods of examination, on perinephritic abscess and on renal infection in infancy and childhood should be particularly helpful. The author has unfortunately failed to include the urea clearance test in the discussion of kidney function testing.

R. K.

ASTHMA AND HAY FEVER IN THEORY AND PRACTICE. In three parts. *Part I. Hypersensitiveness, Anaphylaxis, Allergy.* By ARTHUR F. COCA, M.D., Professor of Immunology, Cornell University Medical College. *Part II. Asthma.* By MATTHEW WALZER, M.D., Instructor in Applied Immunology, Cornell University Medical College. *Part III. Hay Fever.* By AUGUST A. THOMMEN, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College. Pp. 851; 95 illustrations and 7 charts. Springfield, Ill.: Charles C Thomas, 1931. Price, \$8.50.

FROM the standpoint of the student of the phenomena of hypersensitiveness, this is beyond doubt the best book which has appeared on the subject. All three authors bring to their task a thorough knowledge of, and long experience with, the subject. They have spared no pains in setting forth every phase of the subject in the greatest detail. They have surveyed and judiciously culled an extensive literature (over 2000 references). The result is a volume that is truly encyclopedic in its scope. Those working in the field of Allergy cannot afford to be without it. The excellent arrangements of the material and a well-prepared and extensive index make the information easily available to the student and practitioner, so that those not especially concerned with this field need not fear being bogged down by unnecessary detail. After these superlatives the Reviewer will be pardoned if he points out that Dr. Walzer seems at times to tilt rather quixotically against bronchospasm as a factor in the mechanism of bronchial asthma, and that Dr. Coca seems to have adopted a somewhat kindlier view than formerly toward the cutaneous method of testing. He even finds that

with a specially concentrated house-dust extract it is possible for the first time to get positive reactions by the scratch method—we have been doing so to our own satisfaction with a 14 per cent alcoholic extract for the past 11 years. But these are quibbles. The fact remains: this is the number One book in allergy.

R. K.

RECENT ADVANCES IN ALLERGY. By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), Asthma Research Scholar, The Hospital for Sick Children, London. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital; Chairman Medical Advisory Committee, Asthma Research Council of Great Britain. Pp. 432; 98 illustrations, including 4 colored plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$3.50.

BUT merely a review of recent literature as its title would suggest, this book is a well-rounded treatise on allergy. It is the first European book, certainly the first from the British Isles, which is in accord with the views on allergy which are current in this country. The author has also drawn on his own observations in a large number of asthmatic children. The only disadvantage of the book from an American standpoint is its lack of surveys of plant and pollen distribution.

R. K.

QUANTITATIVE CLINICAL CHEMISTRY. VOL. II, METHODS. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, PH.D., Sc.D., Member of The Rockefeller Institute for Medical Research. Pp. 957; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$10.00.

THIS second part of this important work deals with descriptions of the various laboratory procedures concerned with substances studied in clinical diagnosis and therapy (For Review of Part I on Interpretations, see AM. J. MED. SCI., 1931, 182, 275). In general the authors have presented as far as possible gravimetric, titrimetric, colorimetric, and gasometric methods with macro and micro forms, for the numerous substances to be tested. Furthermore they have prefaced each chapter with a discussion of the principles on which the methods are based. The details of Procedure have been printed in black face type, greatly adding to convenience of use. The 32 chapters cover such a breadth of material that space forbids any attempt at detailed description; the excellence of the treatment of the material renders any attempt at critical analysis both superfluous and presumptuous. One can safely say that clinical chemistry will have to make radical changes indeed before these two volumes cease to be indispensable to the student, the clinician and the laboratory worker.

E. K.

PROHIBITING MINDS. By STEWART PATON, M.D., Lecturer on Psychiatry, Johns Hopkins University, Baltimore. Pp. 198. New York: Paul B. Hoeber, Inc., 1932. Price, \$2.00.

A SCIENTIFIC and experienced student of human behavior here shrewdly analyzes the various factors that have led to our present "waves of prohibiting mania." Today's squandered supplies of nervous energy, together with the reluctant recollections of foolish performances by both individuals

and masses, and unwillingness to profit from past mistakes and adapt to present conditions—such forces impel “these feelers, not thinkers” to hate and to try to prohibit anything that runs contrary to their own restricted activities. Such thoughts furnish the author with the material for the first half of his book. Occasional remarks such as “At least three-fourths of the population of the United States are, have been or will be subjects of emotional disorders of sufficient intensity to attract public attention” indicate the gravity of the subject dealt with. The three chief examples of prohibitionism that he discusses are the attempts to regulate the affairs of the Prussian state, Russian communism and the liquor traffic in this country—all failures which drag other evils in their train.

In the last constructive half of the book the author offers his remedies, based on deliberate sustained efforts to “learn to use his mind to help him live more rationally.” The acquisition of more self-control and adaptability will lead to a restored confidence in ability to meet our problems with a corresponding diminution in the prohibiting mania. A thoughtful reading of this penetrating essay is earnestly recommended to those in all walks of life.

E. K.

MENTAL HEALERS—MESMER, EDDY AND FREUD. By STEFAN ZWEIG.
Pp. 363. New York: The Viking Press, 1932. Price, \$3.50.

THIS distinguished illustrator and critic of human types has here engaged to “portray ideas as embodied in certain human lives” identified with bold departures in mental healing. Mesmer, discoverer of the principle of suggestion as strengthening the will-to-health, though he never thoroughly understood his own discovery; Mrs. Eddy, charming away pain and sickness by an ecstasy of faith; and Freud, removing hidden mental conflicts by bringing them into the field of consciousness by the method of psychoanalysis—these three the author without intended partisanship presents as types that have brought healing to many thousands. Most appropriate, therefore, is his quotation from Paul Valéry: “The world becomes of value only through extremes but it exists only thanks to mediocrity.”

Fortunately, for the interest of the tale, it was not possible to maintain the neutral position that the author aimed at. Mesmer is convincingly presented as a maligned philanthropist, the first of the new psychologists in advance of his time, suffering through the ancient and “inexorable commandment that firstlings shall be sacrificed.” The account of Mrs. Eddy, lying between Miss Wilbur’s “rose-colored biography” and Miss Milmine’s now almost unprocurable detraction, should share with Dakin’s “Mrs. Eddy” as an impartial evaluation of the numerous shortcomings yet invincible strength of a woman of genius who carved a position for herself equal in power to Queen Elizabeth or Catherine the Great. For Freud, the author becomes frankly partisan, regarding him as the first to have the insight, sincerity and courage to depart from the ostrich policy of nineteenth century morality of hiding sexual topics that would not down.

But, while granting the value accruing from Mrs. Eddy’s extremes, the author is unsparing of her weaknesses and errors; in the case of Freud he is so in sympathy with the method of relieving suppressed impulses by raising them to the field of consciousness that he overlooks the Freudian exaggerations of Oedipus, narcissistic, castration and other sexual complexes that so mutilate Freud’s doctrine and alienate supporters. Exploration of the “unconscious,” no longer the “unknowable,” is recognized as Freud’s “supreme act of genius,” which is regarded as altering all the standards of our mental dynamics, and as a creation ranking in importance in the story of human knowledge with those of Copernicus and Kant. Perhaps from the exuberance of its partisanship, the exposition of Freudism is the least convincing of the three.

E. K.

BIOCHEMISTRY IN INTERNAL MEDICINE. By MAX TRUMPER, PH.D., Clinical Chemist and Toxicologist, Jefferson Medical College and Hospital, and ABRAHAM CANTAROW, M.D., Instructor in Medicine, Jefferson Medical College. With a Foreword by ELMER H. FUNK, M.D., Sutherland M. Prevost Professor of Therapeutics at Jefferson Medical College. Pp. 454; 11 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$5.50.

"It should be emphasized, that the clinical value of biochemical data depends, first, upon the accuracy of the methods and skillful technique in the laboratory and, second, upon the rational clinical interpretation of the laboratory findings at the bedside. The practising physician is not, as a rule, interested in the first, but he should be well informed regarding the clinical interpretations. This book will serve as a guide. It is generally recognized that considerable skill is required of the physician in the use of laboratory aids to diagnosis and in their proper interpretation in relation to clinical phenomena." "The advancement of our knowledge of the biochemical changes in health and in disease has been most rapid and many of the conceptions of a few years ago have been completely changed or modified. This book will serve to acquaint the practitioner with the recent advances, many of which are to be found only in special monographs and textbooks." (Quoted from Dr. Funk's Foreword.)

MAN AND MICROBES (A CENTURY OF PROGRESS SERIES). By STANHOPE BAYNE-JONES, M.D., Professor of Bacteriology, School of Medicine and Dentistry, University of Rochester. Pp. 128; 17 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$1.00.

THE Century of Progress Series is the outcome of the efforts of the Advisory Committee of the National Research Council to aid the Century of Progress International Exposition in recording as well as depicting the last hundred years of intellectual activity. Here the story of microbes is told in a simple yet accurate manner, in their relation not only to human disease but to agriculture, industry and diseases of animals, plants and insects. Though written primarily for the general reader, it affords not a little that will be new to the average medical reader.

E. K.

INTRACRANIAL TUMORS. By HARVEY CUSHING, Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston. Pp. 150; 111 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$5.00.

THIS stands as a remarkable record of achievement on the part of one who has grown up with neurosurgery and who has directed its development in many ways. From the surgical standpoint the results recorded will be hard for succeeding generations of neurosurgeons to equal, though the author asserts that they will be even better as time goes on. One of its most striking portions has to do with the separation of the gliomas into orderly groups, each with their specific characteristics and each with their own method of reaction. This has greatly reduced the mortality in these invasive tumors. Even in the very malignant multiform spongioblastomas the mortality in the last 50 cases has been only 11.6 per cent. At the other extreme is the record of benign astrocytomas with a case mortality of 4.2 per cent and an operative mortality of 3.5 per cent.

The monograph comprises a study of the glioma, pituitary adenomas, meningiomas (to which term the author still clings), acoustic tumors, congenital tumors (craniopharyngiomas, cholesteatomas, teratomas, chordomas), metastatic and invasive tumors, granulomas, bloodvessel tumors, primary sarcomas, papillomas of the choroid plexus, and miscellaneous tumors. It is well illustrated and planned. It is a book which should be in the hands of every physician regardless of speciality, but it will be most interesting to the neurologist and neurosurgeon. The general practitioner should know it in order to realize the possibilities which neurosurgery offers.

B. A.

THE WHITE HOUSE CONFERENCE PUBLICATIONS ON CHILD HEALTH AND PROTECTION. New York: The Century Company, 1932. *Growth and Development of the Child: Part III. Nutrition.* Report of the Committee on Growth and Development, KENNETH D. BLACKFAN, M.D., Chairman. Pp. 532; various tables and charts. Price, \$4.00.

"NUTRITION implies 'a study of the food substances and of the biochemical processes which utilize them.' This book, therefore, contains both an analysis of the components of diet and an account of the intricate chemistry of the body. The topics of discussion range from an appraisal of the national food supply to the feeding habits of children and the psychologic facts in nutrition."

Obstetric Education. Report of the Subcommittee on Obstetric Teaching and Education, FRED LYMAN ADAIR, M.D., Chairman. Pp. 302; various tables and charts. Price, \$3.00.

"Recommendations are offered to improve obstetric practice and to lower the present high maternity death rate in the United States. Conscious that the high maternal mortality rate is a reflection on the training and education of those who are charged with furnishing maternity care, the Subcommittee made an appraisal of: The training of physicians for obstetric practice, including undergraduate training and subsequent or graduate education, the obstetric education of nurses and nursing attendants; the history, status abroad and status in this country, education and training of midwives; the obstetric education of the laity and of social workers."

THE WISDOM OF THE BODY. By WALTER B. CANNON, M.D., Sc.D., LL.D., George Higginson Professor of Physiology, Harvard Medical School. Pp. 312; 41 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, \$3.50.

THE author's important experiments on the physical effects of the emotions and on the internal balancing adjustments in the body have for years been appreciated by the medical profession, as they have appeared from time to time in medical journals. This comprehensive statement, the first book that he has published since "Traumatic Shock," in 1923, not only will serve as a useful reference and summary for the profession, but should prove interesting and valuable to a wider circle of readers who are glad to get accurate information from a recognized authority on matters that have a wide human application. "The Wisdom of the Body," a title taken from Starling's Harveian Oration, deals with the wonderful adjustments that have arisen in mammals, whereby the "extraordinarily unstable material" of which our bodies are made is coördinated by the two branches of the nervous system and a few other mechanisms into a stable unit capable

of remarkably quick, accurate and efficient adaptations. This relatively constant but dynamic condition, to which the author has given the name, *homeostasis*, is here explored and explained in terms understandable to anyone possessing the simplest familiarity with scientific terms. The epilogue, on Biological and Social Homeostasis, should especially appeal to the philosophically minded. Its inferences, if they could be widely comprehended by our publicists, would be of incalculable value in aiding the social organism to maintain a constancy of existence and in steering it safely through the reefs of our present-day difficulties and anxieties.

E. K.

NEOPLASMS OF DOMESTICATED ANIMALS. (Mayo Clinic Monograph.) By WILLIAM H. FELDMAN, D.V.M., M.S., Division of Experimental Surgery and Pathology, The Mayo Foundation. With a Foreword by CHARLES H. MAYO, M.D. Pp. 410; 193 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.00.

THIS book presents extensive observations on tumors in domesticated animals together with an adequate review of the literature. Theories of etiology, including experimental studies; classification, nomenclature, incidence and general characteristics of animal neoplasms are discussed in the opening chapters. Following these are sections on mesodermal new growths, including those of blood-cell-forming tissues; melanotic and epithelial tumors; the transmissible lymphosarcoma of dogs; experimental studies, and a final chapter on preservation of tissue. This treatise should be of special value in courses on veterinary pathology, and should appeal to all students of neoplastic diseases. Of particular interest are the discussions of tumor incidence in certain species of animals and the apparent susceptibility of various breeds to certain type of tumors.

H. R.

PATHOLOGY FOR NURSES. By EUGENE C. PIETTE, M.D.; Pathologist and Director of the Clinical Laboratories of the West Suburban Hospital, Oak Park, Ill. Pp. 251; 65 illustrations, some in color. Philadelphia: F. A. Davis Company, 1932. Price, \$1.75.

THE insurmountable difficulty of presenting etiology, pathologic anatomy, and clinical pathology in 240 small pages has been met here about as well as can be in books of this kind. It doubtless is as good an adjuvant as can be expected to the equally brief lectures assigned to this subject.

E. K.

LABORATORY TECHNIQUE. By R. B. H. GRADWOHL, M.D., Director, Gradwohl School of Laboratory Technique. Pp. 462; 148 illustrations. St. Louis: Gradwohl School of Laboratory Technique, 1932. Price, \$8.00.

IN spite of the numerous works that have recently been published in this field, this book will doubtless fill a useful corner in many a laboratory. The information is accurate and presented in easily available form. Especially valuable are the newer hematologic methods (hemogram, thick drop, reticulocytes, etc.). Though only 5 pages are devoted to photomicrography and 3 to electrocardiography, these sections are treated as hints on these procedures, which make them useful adjuncts to the usual sources of information. Illustrations are collected at the back, even after the index—a procedure of doubtful value for several reasons. They are entirely original, mostly photomicrographs that really bring out the point they are supposed to illustrate, and constitute an excellent feature of the book. The space gained by the use of small type is mostly wasted by the unnecessarily large margins; the price also seems too high.

E. K.

THE USE OF THE SELF. By F. MATTHIAS ALEXANDER. With an Introduction by PROF. JOHN DEWEY. Pp. 143. New York: E. P. Dutton & Co., Inc.; 1932. Price, \$2.00.

AFTER presenting indorsements by psychologists and the lay press, the writer, his physician having failed to relieve his throat trouble, details a new self-cure system which is in substance that mal-coördination in disease is the result of faulty "feeling" and may be cured by correct "reasoning."

Patients have gone to shrines, to Coué, Mother Eddy, and presumably Sister Aimée has a list of "cures" for ready reference. Nevertheless, substantial progress will continue through regular channels. N. Y.

BOOKS RECEIVED.

NEW BOOKS.

Diseases of the Thyroid Gland. By CECIL A. JOLL, M.S., B.S.C. (LOND.), F.R.C.S. (ENG.), Senior Surgeon to the Royal Free Hospital and the Miller General Hospital; Surgeon to the Cancer Hospital, etc. Pp. 682; 283 illustrations and 24 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, \$20.00.

An Introduction to Zoölogy. By ZENO PAYNE METCALF, D.Sc., Professor of Zoölogy, North Carolina State College. Pp. 425; 184 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.50.

Birth, Stillbirth, and Infant Mortality Statistics for the Birth Registration Area of the United States, 1929. Fifteenth Annual Report. Pp. 373; illustrated with tables. Washington: U. S. Department of Commerce, Bureau of the Census, 1932.

Cancer: Then and Now. Publication of the New York City Cancer Committee, American Society for the Control of Cancer. Foreword by JOHN C. A. GERSTER, M.D., Chairman of Committee. Pp. 80; 35 pages of illustrations. New York: The Chemical Foundation, Inc., 1932. Price, \$1.00. Can be obtained from the New York City Cancer Committee, 34 East 75th St., New York City.

"An instructive and entertaining method of bringing before the public accurate information as to what really is being done and has been done in the way of cancer control."

The Differential Diagnosis of Endocrine Disorders. By ALLAN WINTER ROWE, Director of Research, Evans Memorial, Massachusetts Memorial Hospitals, Boston. Pp. 220; illustrated with tables. Baltimore: The Williams & Wilkins Company, 1932. Price, \$4.00.

Experimental Pharmacology and Toxicology. By HENRY G. BARBOUR, A.B., M.D., Yale University, New Haven. Pp. 141; 14 figures. Philadelphia: Lea & Febiger, 1932. Price, \$2.75.

Excitability. A Cardiac Study. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 208; 15 illustrations. New York: Oxford University Press, 1932. Price, \$3.85.

A New Physiology of Sensation. By W. BURRIDGE, D.M., M.A. (OXON.), Professor of Physiology, Lucknow University. Pp. 70. New York: Oxford University Press, 1932.

Les Réticulocytes et Les Réticulocytoses. By DR. C.-M. LAUR, Préparateur Adjoint à la Faculté de Médecine de Paris. Preface by PROFESSOR N. FIESSINGER. Pp. 160; 3 figures and 4 plates in colors. Paris: G. Doin & Cie, 1932. Price, 35 fr.

Diseases of the Spinal Cord. By WILLIAM B. CADWALADER, M.D., Professor of Clinical Neurology, University of Pennsylvania Medical School, etc. Introduction by WILLIAM G. SPILLER, M.D., Professor of Neurology, University of Pennsylvania Medical School. Pp. 204; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, \$5.00.

The Child and the Tuberculosis Problem. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P., Professor of Preventive Medicine, University of Minnesota; Chief of Medical Staff, Lymanhurst School for Tuberculous Children. With an Introduction by WILLIAM P. SHEPARD, M.D., F.A.P.H.A., Welfare Director, Western Division, Metropolitan Life Insurance Company. Pp. 230; 19 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, \$3.00.

Prospecting for Heaven. By EDWIN R. EMBREE, Pp. 185. New York: The Viking Press, 1932. Price, \$1.75.

Diagnosis and Treatment of Diseases of the Thyroid Gland. By GEORGE CRILE and Associates. Pp. 508; 164 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$6.50.

The Medical Clinics of North America, Vol. 16, No. 2 (Chicago Number—September, 1932). Pp. 272; 47 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Acromegaly. By F. R. B. ATKINSON, M.D., C.M. (EDIN. UNIV.). With a Foreword by SIR ARTHUR KEITH. Pp. 260; 3 illustrations. London: John Bale, Sons & Danielsson, Ltd., 1932. Price, 21s.

"The monograph represents some 20 years interest in the subject of acromegaly on the part of the author. A valuable addition to the book is an interesting and instructive foreword by Sir Arthur Keith, in which his views on acromegaly find expression. The first chapter is devoted to the history of the disease from the year 1550, when a record exists of what was undoubtedly a case of acromegaly, up to the end of the year 1930." The pathologic anatomy, symptomatology, the condition of the nervous system and of the eyes, the metabolic changes, etiology, and pathogenesis receive full consideration in a most praiseworthy systematic compilation.

The Surgical Clinics of North America. Vol. 12, No. 5 (Chicago Number—October, 1932). Pp. 268; 61 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Erdmann's Clinics. Excerpts Selected from the Clinics of JOHN F. ERDMANN, M.D., F.A.C.S., Professor of Surgery in Columbia University, etc. Edited by J. WILLIAM HINTON, M.D., F.A.C.S., Associate Professor of Surgery, New York Postgraduate Medical School (Columbia University), etc. Pp. 315; 39 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$4.50.

A selection of 54 surgical topics, apparently a combination of lectures at the Postgraduate Medical School "supplemented from his Clinics and published articles."

The Colon, Rectum and Anus. By FRED W. RANKIN, B.A., M.A., M.D., F.A.C.S., Division of Surgery, The Mayo Clinic; Associate Professor of Surgery, The Mayo Foundation, J. ARNOLD BARGEN, B.S., M.D., M.S. in Medicine, F.A.C.P., Division of Medicine, The Mayo Clinic; Assistant Professor of Medicine, The Mayo Foundation, and LOUIS A. BUTE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic; Associate Professor of Proctology, The Mayo Foundation. Pp. 846; 435 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, \$9.50.

NEW EDITIONS.

Anatomy of the Brain and Spinal Cord. By WILLIAM W. LOONEY, A.B., M.D., Professor of Anatomy, Baylor University College of Medicine, Dallas, Texas: Pp. 370; 153 illustrations. Second edition revised. Philadelphia: F. A. Davis Company, 1932. Price, \$4.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

The Pathology of Bronchial Asthma.—MACDONALD (*Ann. Int. Med.* 1932, 6, 253) reviews the pathologic findings in a series of 8 autopsies on individuals who had bronchial asthma and who, in 5 instances, died apparently as an immediate result of the seizure of asthma. In discussing the pathology of the condition he notes that the chief local pathologic changes are thickening and hyaline changes of the basement membrane of the bronchi, eosinophilia, muscular hypertrophy and glandular hyperplasia depending upon the individual reaction to vagal (?) stimulation, bronchial sacculation through the mouth of the mucous glands, and epithelial changes such as hypertrophy and metaplasia. The local pathology in this report does not vary very much from the reports made in the immediate past, but of particular interest is the heretofore unnoted constitutional pathology. All of these cases conform in essential detail to the thymicolymphatic constitution, as shown by persistent thymus in every instance, hyperplasia of the lymphoid system, hypoplasia of the adrenals and of the aorta. On the basis of these constitutional findings of disturbances of this particular system the author hypothesizes a theory which he substantiates with his arguments concerning the etiology of bronchial asthma. His contention is that there exists in the asthmatic individual an inheritable hyperplastic type of constitution upon which numerous exogenous factors, ordinarily without influence on normal soil, are able to produce the allergic state, an altered reaction in the soil which is receptive. Frequently an individual may reach midlife before some apparently trivial factor initiates pathologic manifestation of this constitution, as exemplified by asthma. The author discusses rather fully the so-called bacterial asthma, a type of asthma which has been so named because it is assumed that bacteria are the specific allergens because, in turn, some type of allergen must be held, according to the views of some physicians, responsible for asthma. In the absence of any one of the

numerous protein agents which may be responsible for asthma, a bacterium or its protein is assumed to be the excitant. That such is the case seems doubtful because, irrespective of the type of asthma, bacterial or definitely allergic, the pathologic changes are all the same. He agrees with Cooke, who was unable to find any specific allergen in 48 or 50 cases of bronchial asthma, and Zinsser, who confessed to knowing only 1 instance in which the removal of the focus of infection, in this case the sinus, was responsible for relief of asthma. The summary of this paper of 25 pages, rather difficult to abstract briefly, boils down to: The local pathologic changes that occur in asthma, which have been mentioned; the disputation that there is no such thing as bacterial bronchial asthma and last, and most important, asthma and many other allergic phenomena express merely the response of a certain inheritable hypoplastic constitution of the thymicolymphatic pattern to exogenous substances.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,
PHILADELPHIA, PA.

Primary Benign Tumors of the Ureter.—MELICON and FINDLAY (*Surg., Gynec. and Obst.*, 1932, 54, 60) report in detail a case of primary benign ureteral neoplasm, accompanied by a stricture of the ureter, ureteral and renal calculi and marked dilatation and infection of the kidney pelvis and ureter. This combination of lesions has never before been reported. From their studies the authors concluded that primary ureteral tumors are rare lesions which are infrequently diagnosed. The treatment which is safest for the patient and offers him the best chance for a cure is primary nephroureterectomy.

Irradiation of Mammary Cancer With Special Reference to Measured Tissue Dosage.—LEE, POCK, QUIMBY and STEWART (*Arch. Surg.*, 1932, 24, 339) say that pre-operative external irradiation for mammary carcinoma is of value, as is proved by the occasional regression of tumors so treated, by the histologic changes produced and by the better clinical end-results. An efficient devitalizing dose cannot be delivered by external irradiation alone. To deliver an efficient dose one must use interstitial irradiation. The tissue dose delivered to the tumor should be measured and expressed in skin erythema units. This dose should be prescribed. Tables prepared in the physical department enable the clinician to translate into terms of skin erythema units the tissue dose delivered, whether by external or interstitial irradiation. The universal tissue dosage necessary to effect destruction of a radioresistant mammary cancer approximates 12 skin erythema doses. The safest procedure is to treat all patients with mammary cancers with the same sufficient dose, because radiosensitivity cannot always be determined before operation and the same tumor may contain radioresistant and radiosensitive areas. All pre-operative irradiation should be given within 3 weeks or less time. Six weeks should elapse following interstitial irradiations before radial amputation is performed.

Acute Suppurative Pleurisy in Children.—COHN (*Surg., Gynec. and Obst.*, 1932, 54, 696) claims that a study of 123 cases of acute suppurative pleurisy in children and of comparative data indicate that the open method of drainage preceded by repeated aspiration is the choice method of treatment. Simple intercostal incision with open drainage is the preferred procedure in the very sick and in infants; rib resection for all other children. Local infiltration with novocain should be used whenever possible and can be used in most cases. The complications of empyema, and not the disease itself, seem to play the greater part as contributors to the mortality from this disease. Acute otitis media, in some cases complicated by acute mastoiditis, was the most frequent complication. Proper prophylactic care of the nasopharynx is recommended. Diligent after care, next to operative method, is important in surgically treating this disease. The value of operative methods must be measured not by the resulting mortality alone, but by their ability to shorten the period of convalescence, to diminish the incidence of secondary operations and to prevent chronicity.

Carcinoma of Breast.—ALDEN (*Am. J. Surg.*, 1932, 16, 22) states that operable cancers of the breast should be subjected to the radical operation at the earliest feasible moment. The radical operation should consist in a moderate removal of skin, a wide removal of fascia and the removal of both pectoral muscles and the axillary contents. Many patients having obviously inoperable cancers are more comfortable both physically and mentally if external evidences of cancer are removed, although they die of internal metastases. All cases should receive postoperative radiation, for this method of treatment has been improving each year. Every physician seeing cancer cases should study the cases carefully, record their histories in the manner prescribed by the American College of Surgeons. It is only by concerted action and probing facts that progress can be made.

Fistulous Tracts (The Diagnostic Value of an Opaque Medium of Known Contour and Consistency).—WASSON (*Am. J. Surg.*, 1932, 16, 57) writes that the Roentgen ray ureteral catheter is a medium of known opacity and contour. An attempt is made to draw attention to its use as a simple though valuable diagnostic aid in the study of fistulous tracts, a piece of apparatus ready at hand. Its use is indicated in the injection of those fistulas whose distribution and location are unknown and when it is therefore undesirable to use an opaque liquid or paste. It is always desirable to study the tissue surrounding the tract or cavity, and the catheter obscures this less than the usual other media. In cases presenting more than one fistulous opening, the use of more than one medium of known contour permits ready and quick recognition of each tract and aids in the differentiation of one from another.

Maggots in the Treatment of Chronic Osteomyelitis, Infected Wounds and Compound Fractures.—LIVINGSTON (*Surg., Gynec. and Obst.*, 1932, 54, 702) believe that there can be no question as to the healing value of the maggots or larvæ treatment in all forms of chronic osteomyelitis, infected wounds and complications following fractures. The interest

aroused by the results obtained would naturally lead to an investigation of the reason for the effectiveness of this treatment. Experimental work would seem to show that it is not merely the mechanical action of the maggots, *i. e.*, feeding, rapid movement, etc., in the wound, but rather that some additional agent is developed that aids in the healing process. This conclusion seems warranted when we consider that paste made from the dead bodies is also effective as a curative agent. That additional agents are probable in effecting the cure seems to be clearly demonstrated by the use also of filtered extracts from the bodies of the dead larvæ. This would seem to point clearly to the presence of some agent which in itself is sufficiently powerful to overcome infections and permit the normal hydrogen-ion concentration balance to be established. The agent believed to effect this result is a bacteriophage. This opinion is warranted from the fact that filtered uncontaminated products derived from the bodies of larvæ in culture were quite as suitable as the living maggot, and from the fact that when these cultures were brought into contact with pyogenic organisms in petri dishes cultures were destroyed.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE,
NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,
BOSTON, MASS.

A New Method of Treatment of Typhoid Carriers.—Among the measures used for the prevention of typhoid epidemics the effective treatment of typhoid carriers plays a prominent rôle. None of the methods used in the past are reliable in their effects. ONODERA, MURAKA WA and LIU (*Deutsch. Arch. f. klin. Med.*, 1931, 171, 503), utilizing the sensitivity of the typhoid bacilli to the action of halogen compounds, and taking advantage of the fact that following the intravenous administration of tetraiodophenolphthalein, according to the technique used in cholecystography, the concentration of the substances in gall bladder is usually 5 to 8 per cent, claim that this method is useful in the treatment of typhoid carriers with infected gall bladder. *In vitro* experiments indicated that a 3 per cent solution of tetraiodophenolphthalein kills the typhoid bacilli within 24 hours, a 4 per cent solution within 12 hours, a 5 per cent solution within 10 hours and 6 per cent solution within 6 hours. Although the exposure of these solutions to Roentgen ray radiation did not alter the effectiveness of the tetraiodophenolphthalein, the authors claim that, nevertheless, the Roentgen ray exposure of the patients after the ingestion of the tetraiodophenolphthalein similarly to the technique used in cholecystography insures the effectiveness of this method of treatment. This

method is not invariably successful. Of 7 typhoid carriers 3 became permanently sterile of typhoid bacilli, 2 showed negative cultures only for 1 month and in 2 cases the method was ineffective.

The Treatment of Obesity.—Those who habitually overeat do not necessarily become overweight. There is considerable evidence that the average normal individual disposes of the excessive caloric intake by burning it up and eliminating it as heat. The principles of losing weight include decreasing the caloric intake, increasing physical activity, administration of hormones, drastic purgation and the encouragement of sweating which may yield but short-lived effects. LYON and DUNLOP (*Quart. J. Med.*, 1932, 25, 331) studied particularly the comparative value of subcaloric diets and of thyroid extract on 35 patients of different types of obesity. The mean weight of the cases was 69 per cent above the average. All the subjects, including marked endocrine cases, lost weight while dieting. It has been found that the rate of weight-loss bears a definite relation to the caloric value of the diet: the smaller the diet the more the loss. The rate of loss is greatest at first and decreases as the diet is continued. If the total caloric intake is kept constant at 1000 the weight loss is greatest when the carbohydrate of the diet is low. It has been found that 9 grains of thyroid extract are required in order to produce a loss of weight equal to that caused by the standard 1000 calorie diet. The effect of the thyroid is proportionate to the dose given. The basal metabolic rate for the series of cases was usually within normal range on admission. The rate usually fell during the period of undernutrition, and was raised about 20 points during the administration of thyroid extract. The loss of weight when the patients were taking low diets appears to be due to the removal of fat and water from the body, but when thyroid is given the utilization of fat represents a smaller fraction of the weight loss, while the proportion of water removed from the body is greater, and some of the loss may be due to a negative protein balance.

Some Significant Observations on the Occasional Unsterility of Alcohol Solutions.—There is a general tendency to consider alcohol solutions used in surgery and medicine as necessarily sterile. Often other more reliable sterilizing agents are not used because of the belief in the absolute germicidal action of alcohol. There is some literature available in the past that that is not the case. KUHN and DOMBROWSKY (*München. med. Wchnschr.*, 1932, 79, 791) now report an observation of great practical significance. During an investigation of the explanation of a contamination of "sterile" catgut these authors undertook to determine whether or not alcohol, benzin and ether are necessarily sterile. They arrived at the conclusion that all these disinfectant solutions may be contaminated, particularly from containers which are not sterilized. In certain solutions of 70, 80, 90 and 96 per cent solution of alcohol they were able to demonstrate aërobe and anaërobe spore-containing organisms. Of 40 examined alcohol solutions only one-half were sterile. The other half contained *Bacillus subtilis*, *Bacillus subtilis similis*, *Bacillus mesentericus*, etc. They could trace the source of these bacteria to the barrels from which the alcohol solution was made up. Similarly they observed that benzin and ether solutions

may be contaminated. They advise, therefore, that the containers and the water with which the alcohol is diluted should be sterilized. If alcohol is used to preserve catgut, this alcohol should be redistilled and special caution should be taken that the glass ampules are sterile. In another article KNORR (*München. med. Wchnschr.*, 1932, 79, 793) reports his experiences on the spore content of alcohol solutions. He gives the earlier literature dating back of 1881 that points out that the commercial alcohol is not sterile. Such alcohol solutions may contain spore-bearing bacteria, but they may contain also other contaminations from the air. Thus he was able to demonstrate that a 70 per cent alcohol solution may contain *Bacillus subtilis*, *Bacillus mesentericus*, *Bacillus mycoides*, etc., and that these organisms grew rapidly on liver and sugar cultures. The author was able to demonstrate active spores from as small an amount as 1 cc. of alcohol solution. He advises that the alcohol solution used in surgery and medicine should be distilled under the sterile condition. The water should be also free especially of spore-bearing organisms and sterile precautions should be followed in the keeping of the alcohol solution.

NOTE.—Preparation of 70 per cent alcohol by dilution of the official 95 per cent with tap water was found by one of the editors (S. W.) to yield solutions containing living organisms. These solutions of 70 per cent alcohol did not spontaneously become completely sterile until at least 3 days had elapsed.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Diagnosis of Early Poliomyelitis.—GORDON (*J. Am. Med. Assn.*, 1932, 99, 1043) says that two benefits are the result of the recognition of poliomyelitis in its preparalytic stage. The public health is benefited by isolation of affected individuals at the earliest possible time. The second advantage is to the patient through early institution of treatment, whether it is carefully prescribed rest in bed, reduction of pressure by drainage of the cerebrospinal fluid or the use of supposed specific measures. Preparalytic poliomyelitis is a clinical entity distinguishable from similar conditions with a certain degree of sureness. The facts contributing to clinical recognition have been repeatedly emphasized, and yet practical experience indicates that there is a need for better general appreciation of the clinical nature of this disease. It is too often first recognized by the presence of paralysis. It is also unfortunate that in an epidemic there is a tendency to advance the diagnosis of poliomyelitis for many other and more common diseases of childhood without sufficient critical differentiation. This circumstance leads to unsatisfactory management of conditions that are not poliomyelitis, and to undue alarm about the prevalence of the specific infectious disease. The diagnosis of early poliomyelitis depends on a sound clinical suspicion substantiated by evidence derived from exami-

nation of the cerebrospinal fluid. Epidemiologic evidence aids diagnosis as cases are known to be more prevalent in August, September and October, with young children more affected than older age groups. The symptoms are those of many general infections, including typically a low grade fever, headache and vomiting. Three outstanding physical signs give the greatest aid. They are stiffness of the neck, rigidity of the spine and ataxic tremor of the extremities. The diagnosis is primarily clinical. When the evidence suggests poliomyelitis and other possibilities have been eliminated, confirmation is secured by lumbar puncture at the proper time. The cerebrospinal fluid in poliomyelitis is essentially clear, rarely of greater turbidity than slight haziness. Laboratory differentiation thus resolves itself into distinguishing infections of the central nervous system characterized by clear fluids.

The Value of Salmon Oil in the Treatment of Infantile Rickets.—ELIOT, NELSON, SOUTHER and CARY (*J. Am. Med. Assn.*, 1932, 99, 1075) treated with salmon oil 13 children with active rickets. They recorded the response to the treatment as shown by clinical examination, roentgenograms and determinations of blood calcium and phosphorus. The oil used had been prepared from the waste products of three species of salmon, the Pink or Humpback, the Chinook or King, and the Sockeye or Red. The oil was given in doses of from 10 to 20 cc. a day, the average amount being 13.8 cc. It was well taken and well tolerated by the entire group. Response to treatment as shown by roentgenographic and blood studies was very prompt and advanced healing was brought about in from 3 to 9 weeks. Of the 6 children whose blood was studied after from 6 to 8 days of treatment, 5 showed definite increase in the serum calcium level or serum phosphorus or both. In 2 cases a normal level was reached by the end of the second week. Three children who were examined for the first time after 2 weeks from the original examination showed a return in serum calcium and phosphorus to the normal level. Only 1 child showed a greater delay in responding to the treatment. Roentgenographic evidence of response to treatment was equally prompt, 7 children showing the fresh lime salt deposits in 1 week, and 5 others in 2 weeks. One child did not show fresh deposits until the end of 3 weeks. Craniotabes improved rapidly under treatment with salmon oil. Biologic-assays were made of the 3 specimens of salmon oil that were used. They showed that the Chinook and Sockeye oils were nearly equal in vitamin A potency to a composite sample made from medicinal cod-liver oils, and that Pink oil was distinctly inferior in vitamin A potency. The Sockeye and Pink oils contained twice as much vitamin D as the composite cod-liver oil, and the Chinook sample about 50 per cent more than the same sample of cod-liver oil. There is approximately 1,000,000 gallons of salmon oil available through the salmon canning industry of the Pacific states and Alaska. About three-fourths of this would come from the species of salmon used in this study and shown to be potent in the cure of rickets. About 370,000 gallons would come from the species of red salmon known to be high in vitamin A as well as in vitamin D. The production of salmon oil at low cost would be of special value at this time when the nutrition of many infants and children is suffering from lack of proper and adequate food.

Scarlet Fever.—PEACOCK, WERNER and COLWELL (*Am. J. Dis. Child.*, 1932, 44, 494) examined 258 adults and found hemolytic streptococci in 72 (28 per cent) and 45 (17 per cent) gave positive skin reactions to the Dick test. Forty of the 45 who gave positive skin reactions received toxin for immunization. Of those retested, 87.5 were immunized to the point of negative skin reactions. On the basis of both time off duty and symptomatology, 15 per cent of the people immunized experienced severe reactions. Approximately 85 per cent of the subjects receiving injections of toxin had more or less distinct reactions. Hemolytic streptococci had disappeared from the nose and throat of 92 per cent of the subjects surveyed at the end of 28 days. Only 15 per cent of the susceptible individuals as determined by the Dick test harbored the organisms. Among the 258 subjects with positive or negative cultures, the number with tonsils and that in whom tonsillectomy had been performed were approximately equal. The erythema of the skin test averaged 19 by 18.6 mm. in diameter, and its size bore no particular relation to the grade of reaction experienced by the adults immunized. Of the adults who gave negative skin reactions, 70 per cent gave no history of scarlet fever, 24 per cent gave a history of having had the disease, and 6 per cent furnished records with no data available on that question. If the chocolate agar medium is a reliable means of differentiating nonscarlatinal from true scarlet fever streptococci, then 56.9 per cent of the organisms isolated in this series should be classified as related to scarlet fever. If the opsonification test is of differential value, 43 per cent of the organisms isolated were of scarlatinal origin, an agreement of 80 per cent with those giving no reaction on chocolate agar. Among the 186 individuals giving negative skin reactions to the Dick test, no definite case of scarlet fever developed. Of the 40 adults giving positive skin reactions, 2 contracted scarlet fever before the series of immunization was completed. Of the 5 subjects who were not immunized, 2 had severe attacks of the disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

VAUGHN C. GARNER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Stovarsol in the Treatment of Syphilis in Infants and Children.—Since very few studies in the treatment of syphilis by stovarsol have been carried on this country, the paper by ROSENBAUM (*Am. J. Dis. Child.*, 1932, 44, 25) dealing with the use of the drug in 41 children with prenatal syphilis is both interesting and timely. The dosage and system employed were those of Bratusch-Marrain, who advocated 0.005 gm. of stovarsol per kilogram of body weight for 7 days, then

0.01 gm. for 7 days, 0.015 gm. for 7 days and 0.02 gm. for 42 days, followed by a rest period of from 4 to 6 weeks. The above-mentioned courses and rest periods are repeated until the serologic tests are negative and three times thereafter. Then a rest period of 6 months is given, followed by one additional course. Stovarsol is given exclusively by mouth as an odorless white tablet readily soluble in water or milk. In 9 patients whose treatment was begun during the first year of life and continued for a year or more, serologic reversal was obtained in all cases and the clinical results were excellent. The author points out that in a similar group of 34 patients treated by the method of sulpharsphenamin and mercury, 26 per cent were Wassermann-fast at the completion of treatment. In 6 patients who were more than 1 year of age when treatment was begun and in whom it was continued for a year or more, serologic tests became negative in only 50 per cent, though clinical results were excellent. The remainder of the cases studied were under treatment for less than 1 year. Clinical improvement occurred in all patients. The serologic tests were reversed or influenced in most cases.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CHARLES C. NORRIS, M.D.,

PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.,

AND

FRANK B. BLOCK, M.D.,

SURGEON, JEWISH HOSPITAL, PHILADELPHIA.

Cancer and Weight.—At the Huntington Memorial Hospital a study of 475 cases of epidermoid carcinoma of the cervix in which radium treatment was used has been made by LUND (*Arch. Surg.*, 1932, 24, 145) for the purpose of determining the relationship between the prognosis of the case and the weight of the patient. He found that the percentage of cures of patients with approximately normal weight was twice that of patients who were much over or much under normal weight. A group of 79 patients with adenocarcinoma of the cervix or fundus was similarly studied, and a definite but less marked relationship was found. The obvious explanation for the unfavorable prognosis in the underweight patients is that many of them are in the terminal stages of the disease, but the reasons for poor results in fat patients are not so obvious. One factor probably is the purely mechanical difficulty of applying radium accurately in fat patients. Further than this it is purely speculative as to whether the fat person has less resistance or offers a more fertile field for malignant growth.

Diagnosis of Gonorrhea.—In an effort to determine the value of laboratory aids in the diagnosis of gonorrhea in women, JACOBY (*Am. J. Obst. and Gynec.*, 1932, 23, 729) made a detailed study of the results

of such examinations. He believes that repeated smears should be taken and carefully examined, but the use of Gram's stain is not essential since in conjunction with a proper evaluation of the clinical examination the methylene blue stain is adequate for practical purposes. A positive smear is conclusive evidence of infection, but a negative smear, even when repeated, does not exclude the presence of a gonococcal infection. Suspicious organisms, extracellular or intracellular, should be interpreted with the clinical evidence, while pure spreads of pus cells, even without organisms present, should be regarded as suspicious evidence of gonococcal infection. Positive cultures are conclusive criteria, but are not practical or well adapted to routine practice, but a negative culture does not exclude the presence of a gonococcal infection. The complement fixation test is unreliable with the present technique since neither positive nor negative findings are conclusive and, therefore, the test in its present form should not be used. From the above opinions it is apparent that he believes that laboratory procedures are of minor importance in establishing a diagnosis of gonorrhea in women and the chief reliance should be placed upon the history and clinical evidence.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.,

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,

AND

H. P. WAGENER, M.D.,

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

Ophthalmologic Importance of Focal Infective Prostatitis.—PELOUZE (*Arch. Ophthalm.*, 1932, 7, 372) believes that no study of focal infection in the male is complete without investigation of the prostate. After the age of 30 years prostatitis is usually an infection secondary to a distant focus, predominantly in the teeth or tonsils. Occasionally it is caused by gall bladder disease, by influenza or by some other systemic infectious disease. In a series of 100 unselected cases of focal infective prostatitis with distant absorptive symptoms, only 7 patients had ever had gonorrhea, 69 had infected tonsils, 61 had infected teeth and 46 both. Of all men with symptoms of a focal infection 72 per cent have prostatitis and at least 35 per cent of all men above the age of 35 years have prostatic infection. Infections of the nasal accessory sinuses are not important primary foci for prostatic infections. Focal infective prostatitis usually gives no subjective symptoms and its diagnosis rests solely on the microscopic study of the digitally expressed prostatic secretion. It does not recover spontaneously and it cannot be cured by local treatment until the causative foci have been removed. In the treatment of prostatic infection associated with ocular lesions the prostate should not be massaged oftener than twice a week and not

within 3 days of the subsidence of a focal reaction caused by a previous treatment. Treatment should be continued for at least 3 months. While true gonorrheal iritis is very rare, a large percentage of focal infective ocular lesions, such as ulcerative keratitis, iritis, uveitis and choroiditis are caused primarily, or more often kept up secondarily, by prostatic infection. The relationship can be demonstrated by the occurrence of a focal reaction in the affected eye following manipulation of the prostate. If such a reaction does not occur following one of the first few treatments the prostate can be practically acquitted as a focus. In subsequent treatments the massage should be so graduated as to prevent the occurrence of any or at least of too severe a reaction. If the eye condition becomes worse in spite of careful massage, the treatment should be temporarily discontinued. If the eye condition improves at first and later remains stationary search should be made for recurrent foci elsewhere, in the teeth, tonsils or nasal accessory sinuses. Massage of the prostate should not be continued while any vaccine is being administered to the patient.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Glossitis in Pernicious Anemia.—In reporting 2 personally encountered cases, MAGER (*Monatschr. f. Ohrenh.*, 1932, 66, 315) emphasizes the importance of glossitis as an early clinical manifestation of pernicious anemia; and of making thorough hemocytologic examinations in all instances of glossitis and stomatitis. Subjectively, intermittent lingual and buccal pain, burning and soreness—intensified by ingestion of hot and highly acid foods—were the chief symptoms. Objective findings consisted of a thickened tongue with a smooth, inflamed-looking surface and edges. At times lingual, palatine and buccal vesicles occur.

A New Test for the Diagnosis of Disease of the Inner Ear.—Movement of the ears on acoustic stimulation may be voluntary or involuntary. As a voluntary act, it is usually associated with intent listening and often has been designated as "pricking up the ears." Involuntary auricular movement occurs in animals and man. In the experimental animal it is called Preyer's reflex, which is commonly accepted as physiologic proof of auditory integrity. This reflex movement has also been discerned in persons presenting pathologic conditions of the auditory apparatus. This involuntary phenomenon in human beings has been termed the "auricle reflex" by FABRICANT and SOMMER (*Arch. Otolaryngol.*, 1932, 16, 360). Inasmuch as, apparently, no practical clinical utilization of this reflex in man has been made, these authors produce evidence to show that the "auricle reflex" is not rare and of some diagnostic significance. The "auricle reflex" is a rhythmic jerking of the auricular appendage. Usually the movements are confined

to a portion of the auricle; if the excursions involve the entire ear, they are of small amplitude—as a rule. The reflex best can be elicited by holding the middle C 1 tuning fork to the concha, or by placing over the forehead or mastoid prominence. A positive “auricle reflex” was encountered in 55 of 198 cases. In only one of the 55 was the ear apparently normal. The reflex occurred more frequently in patients with lesions of the inner ear than in those with combined involvement of the middle and inner auditory apparatus. No movement was noticed in persons with unilateral cochlear lesions, otosclerosis or complete deafness. Having observed that the “auricle reflex” most frequently associated with progressive deafness, the authors explain its mechanism on the basis of increased tonus of the auricular musculature. They conclude that the presence of the reflex should suggest a primary involvement of the cochlear nerve.

RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.,

AND

CHARLES G. SUTHERLAND, M.D.,
CONSULTING PHYSICIANS, SECTION OF ROENTGENOLOGY, MAYO CLINIC,
ROCHESTER, MINN.

Radiotherapy of Pituitary Tumors.—Thirteen cases of pituitary tumor were subjected to Roentgen ray therapy and observed at tri-monthly intervals by HARRIS and SELINSKY (*Radiology*, 1932, 18, 777). Seven of the 13 patients were distinctly benefited by the treatment and 1 showed temporary improvement. Amelioration of headache and improvement in vision were most frequently noted. In no case did the symptoms completely disappear. Failure to respond to treatment is highly suggestive of a cystic tumor (craniopharyngeal pouch cyst).

Recent Advances in Heliotherapy as Applied in Pulmonary Diseases.—It is a generally accepted tradition, says FORSTER (*Arch. Phys. Ther., X-Ray, Radium*, 1932, 13, 214), that while heliotherapy is efficacious in extrapulmonary tuberculosis its use is contraindicated in the pulmonary form of the disease. He feels that the explanation of this fundamental mistake lies in overdosage, and that it is most essential to study and supervise most carefully the reaction of the individual patient. He has noted many times that certain patients were unable to take more than a few minutes of sun. If a patient with tuberculosis of the wrist receives an overdose of sun he will undoubtedly sustain a reaction which may be unfavorable, but the damage is not irreparable. When pulmonary tuberculosis is being treated by heliotherapy and an unfavorable reaction is produced the harmful effect may continue indefinitely. The author chooses for treatment those patients with pulmonary disease who have already shown power to resist their toxemia. Patients with acute advancing pulmonary tuberculosis can only expect harm from sun treatment, but as soon as the

disease has shown evidence of developing chronicity, which is the beginning of cure, then carefully supervised heliotherapy almost invariably has a favorable effect on metabolism and is an aid to the patient in acquiring resistance to the disease. When patients show marked sensitivity to sun treatment lamps may be used until tolerance is built up to the point where the sun can be borne. In spite of the efforts of lamp manufacturers to reproduce all the elements of the spectrum, it is becoming recognized that natural heliotherapy has advantages over any other form of light treatment.

Pulmonary Asbestosis. — The fact that the inhalation of asbestos dust produces an effect on the lungs was observed many years ago, but the serious results which follow have only recently been recognized. SPARKS (*Radiology*, 1931, 17, 1249) considers the roentgenologic appearances quite typical in advanced cases. The movement of the diaphragm is limited and its outline tends to be indistinct or uneven. There is clouding in the costophrenic angle due to pleural thickening which latter often extends along the costal margin to the apices. The lung fields at first show slight increase of density in the lower zones without accentuation of the bronchial markings. Sometimes small calcareous deposits are scattered through the lower zones, but they are less dense and more irregular in outline than calcifying tubercles. Later, dense patches and a fine network of fibrosis appear in the lower zones and may extend into the mid zones.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,

AND

GEORGE JOHNSON, M.D.,

INSTRUCTOR IN PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
DENVER, COLORADO.

On the Problem of Delinquency. — LEVY (*Am. J. Crim. Law*, 1932, 3, 197) lists three major groups of influence responsible for delinquency: (1) Social forces; (2) personality traits, and (3) mental conflict. Rarely does one group predominate; usually it is a mixture of two or all three groups, with the balance in favor of one or the other group. He cites examples to illustrate the part played by the different causal factors and concludes with the statement that when these factors are determined and grouped, treatment can be easily instituted in logical relation to them.

Creation and Handling of Resistance in Clinical Practice. — ALLEN (*Am. J. Orthopsychiat.*, 1932, 3, 268) defines resistance as the effort made by individuals to handle negative feelings manifested mainly by antagonism, distrust, dislike, and so forth, and it is held by the author that full participating coöperation cannot be had until these resistive manifestations are allowed free expression. We should see an individual as one with a problem of his own and act as clarifiers, not cor-

rectors, which happens when we project our own ideals into the treatment program and insist that the patient be moulded according to our own point of view. Oversympathy with the patient may create resistance in the parents which will be directed against the clinic. We can avoid creation of resistance by seeing the problem objectively by allowing full and free expression of negative feelings. No clinic member should show force, coercion, blame, shame or any feeling that would suggest anything but an unbiased observer with a desire to help.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

The Occurrence of Intranuclear Inclusions in Monkeys Unaccompanied by Specific Signs of Disease.—COVELL (*Am. J. Path.*, 1932, 8, 151) found intranuclear inclusions in 20 out of 60 monkeys. The animals were dead of various diseases. The inclusions were located in nasal mucosa (6 cases), tracheobronchial mucosa (5 cases), alveoli of the lungs (12 cases) and intrahepatic bile ducts (3 cases). The inclusion nuclei were characterized by margination of all basophilic chromatin on the inner surface of the nuclear membrane, clumping of the acidophilic material in the center of the nucleus and the appearance of a clear halo between the inclusion and the nuclear membrane. The author assumes that these inclusions represent the presence of an unknown virus infection of low virulence and points out the importance of being aware of the spontaneous occurrence of such inclusions in an animal like the monkey which is used so much in the study of filtrable viruses. This report comes as a sequel to that of STEWART and RHODS (*Proc. Soc. Exper. Biol. and Med.*, 1929, 26, 664) who were first to describe spontaneous inclusions in monkeys.

Polypi Coli.—Polypi of the colon are found in two conditions: The first, polyposis coli universalis, occurs in the young adult or adolescent and manifests itself in a large number of adenomatous polypi thickly scattered over the whole length of the colon. Polypi coli, on the other hand, are seen most commonly in later adult life, and are found in small numbers. Histologically the lesions in the two conditions are similar. In 1100 consecutive autopsies studied by SUSMAN (*J. Path. and Bact.*, 1932, 35, 29), 65 cases of polypi coli (with a total of 198 polypi) and 1 of polyposis coli universalis were encountered. The polypi did not have any particular site of election in the colon. The well-known relation to carcinoma was substantiated—of the 66 cases 15 had carcinoma of the large bowel. Viewed from the opposite standpoint, 34 cases of cancer of the colon came to autopsy during the period covered by this investigation. In 15 of these, polypi were also present and in 5 of the

15, actual malignant polypi were found. The sex distribution showed a distinctly higher incidence in males (77 per cent). Of the patients with polypi coli 93 per cent were over 40 years of age.

The Dynamic Bronchial Tree.—MACKLIN (*Am. Rev. Tuberc.*, 1932, 25, 393) studied the movement of the lung by means of the Roentgen ray and anatomic dissection. He found that the lung root constituted a pedicle from the bifurcation of the trachea to the roentgenologic hilum. It is normally flexible, permitting the air and blood channels to stretch and widen in inspiration and to shorten and narrow in expiration, but this flexibility may be impaired by pathologic processes, and then the function of the lung is handicapped, particularly in the region lying above and behind the hilum, that is, in the district which is preferred by the tuberculous process. The connection of root movement restriction with the precipitation of tuberculous lesions is suggested. Diagrams are employed to clarify the ideas presented. Need for further Roentgen ray research to ascertain the normal range of root movement under all conditions is emphasized.

Bacteriological Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis.—A careful bacteriologic investigation of the blood, synovial fluid and subcutaneous nodules in patients suffering from rheumatoid arthritis has been recently completed by DAWSON, OLMSTEAD and BOOTS (*Arch. Int. Med.*, 1932, 49, 173). Using the elaborate technique of Cecil, Nicholls and Stainsby, 105 blood cultures were made on 80 patients. Blood from healthy individuals and sterile agar were used as controls. The organisms obtained by this method, the majority of which were coarse Gram-positive bacilli, diphtheroid forms and staphylococci, could not be regarded as of any etiologic significance, and were also frequently present in the control material. Aërobic and anaërobic cultures of 23 specimens of synovial fluid and 12 subcutaneous nodules yielded similarly negative results.

The Relation of the Liver to the Disposal of Hemoglobin.—The deposition of iron pigment in the liver, kidney and spleen was studied by MUIR and YOUNG (*J. Path. and Bact.*, 1932, 35, 113) by injecting solutions of hemoglobin into rabbits. After a single injection of a considerable amount there was no evidence of the hemoglobin being taken up by the liver cells or Kupffer cells. Nor was there any present in the bile. On the other hand, the cells of the convoluted tubules of the kidney gave a diffuse reaction for iron on histologic examination. The spleen did not show any significant change. The next step was the study of "chronic hemoglobinemia" caused by daily intraperitoneal injections of the hemoglobin solution. In these experiments the liver did show a slight increase in iron, which was accumulated mostly around the central veins, but the amount was not nearly so great as in the anemia produced by a hemolytic serum. The kidney contained a great deal of hemosiderin, nearly all of which was in the proximal convoluted tubules. The spleen also contained an increased amount of hemosiderin over the normal. The authors conclude that these experiments do not support the view that hemoglobin as such is taken up by the cells of the liver and broken up by them.

Psittacosis: Report of 5 Cases.—An outbreak of psittacosis, 5 cases in one family, traced directly to a group of parakeets imported from Cuba by a returning tourist, was studied by RABINOWITZ and LIVINGSTON (*Arch. Int. Med.*, 1932, 49, 464). Two of the patients died. Analysis of the histories of the 5 cases brought out the following important features. The incubation period was about 9 days. The disease was insidious in its onset, beginning with chilly sensations, malaise and fever. The patients soon became decidedly toxic, but pulmonary signs did not appear until the disease was well advanced. Roentgen ray showed dense well-defined consolidation of part of a lobe; crepitant râles in the involved area. Slight cough was usually present, accompanied by scanty, extremely thick, mucoid expectoration, occasionally blood-tinged. The leukocyte count ranged between 9000 and 13,000, with relative increase of polymorphonuclear cells. An outstanding feature was the tendency to venous thrombosis. In the one postmortem examination the important findings were lobular pneumonia, thrombosis of the pulmonary artery, pulmonary veins, iliac vein and splenic vein, gastroenteritis and multiple hemorrhages of the spinal cord with chromatolysis, satellitosis and fat replacement of the anterior horn cells. The psittacosis virus was demonstrated in the liver, lungs and spleen. It was also found in the sputum of one of the patients and in the liver and spleen of one of the parrots. Incidentally, this bird was apparently healthy.

A Case of Reticulum Cell Carcinoma of Thymus.—McDONALD (*J. Path. and Bact.*, 1932, 35, 1) studied a tumor, which formed a pedunculated, cystic mass, measuring 6 by 4 cm. in area, and was located immediately below the great vessels as they leave the heart, in a male, aged 59 years. The tumor had a well-defined fibrous capsule, and the parenchyma was diffuent and grayish-red, suggesting a necrotic condition. Microscopically the two main types of cells were seen. The first was a large round, oval or polyhedral "epithelioid" cell very similar to the reticulum cell of the thymus. Scattered among these cells were others morphologically identical with small lymphocytes. The "epithelioid" cells grew in strands in close relation to the vessels; in some places they were arranged in flattened plaques almost like squamous epithelium. There was no tendency toward an alveolar or perivascular arrangement of the parenchyma. On the whole, there was a slight superficial resemblance to the medulla of the thymus, although Hassall corpuscles were absent. There were also some inflammatory changes. The tumor was only locally malignant, there being no distant metastases or infiltration of the neighboring lymph nodes. There were some deposits in the adipose tissue at the tumor base, but these were considered to be portions of involuted thymus. A single Hassall corpuscle was found in one of these deposits.

Sacculated Intracerebral Aneurysm of the Middle Cerebral Artery.—A case is reported by CHASE (*J. Path. and Bact.*, 1932, 35, 19) of a single, sacculated aneurysm arising in the middle cerebral artery and situated entirely within the brain substance. The patient was a woman, aged 30 years, 8 months pregnant. The only complaint had been a persistent, dull, generalized headache for the preceding 6 months. She was

admitted in coma, and died on the operating table after a Cesarean section had been performed and a healthy, live baby delivered. At autopsy the ruptured aneurysm, measuring 3.2 cm. at its greatest diameter, was found. There was also an anomalous distribution of the vessels at the base of the brain—absence of both posterior communicating arteries and anomalous position and branching of both anterior choroidal arteries. The author discusses the three possible etiologic factors: (1) inflammation, (2) degenerative changes and (3) congenital structural malformations. He decided that the latter was the important factor in this case. This decision is reached by exclusion of the first two and the presence of developmental vascular malformations. In addition to those mentioned above, definite defects in the media of two vessels at the acute angle of branching were found; it is assumed that the aneurysm arose in a similar weak point at the division of the right middle cerebral artery into its three large cortical branches.

Histochemical Studies by Microincineration of Normal and Neoplastic Tissues.—Comparative histochemical studies of normal and neoplastic tissues by an improved method of microincineration were undertaken by SCOTT and HORNING (*Am. J. Path.*, 1932, 8, 329) with the confirmation and extension of the earlier observations of Policard and Doubrow in this field. Several types of human breast carcinomas along with three varieties of transplantable mice tumors and normal control tissue were subjected to incineration in an electric quartz oven at 650° C. and the inorganic residue studied in dark field illumination. Apart from cancerous tissue remaining carbonized longer than normal tissue, it was observed that the distribution of the mineral ash deposits was more abundant and concentrated in the tumor than in the surrounding stroma. Both nuclei and cytoplasm of the tumor cells moreover contained more ash than normal cells, the deposits being concentrated toward the periphery of the nuclei, which also contained more iron oxid than seen in the controls. The difference in ash content between the neoplastic tissue and the stroma was also observed in the rodent tumors but was not so striking as in the human material. The authors felt that their results demonstrate the functional differences between cancerous growths and normal tissues, and that a close similarity exists between the distribution of the mineral salts in embryonic and malignant cells.

Subcutaneous Nodules in Chronic Arthritis.—An histologic and bacteriologic investigation of the subcutaneous nodules occurring in chronic arthritis has been carried out by CLAWSON and WETHERBY (*Am. J. Path.*, 1923, 8, 283). These structures, which varied in size from 5 mm. or less to 3 cm., were present in 29.5 per cent of 200 cases. They were found most frequently in the upper extremities, were often multiple and sometimes occurred bilaterally in the same location. In the gross, areas of necrosis surrounded by fibrous tissue were usually seen. Microscopically these necrotic areas contained many polymorphonuclear leukocytes and were surrounded by mononuclear and multinuclear cells, often showing a palisade arrangement similar to that seen in the heart valves in rheumatic endocarditis. Small abscesses containing streptococci were also frequently noted. A perivascular inflammatory

response accompanied by endothelial swelling was present. The nodules were surrounded by varying amounts of fibrous tissue. The strong similarity noted between these structures, the subcutaneous nodules of rheumatic fever and those experimentally produced by streptococci of low virulence suggest to the authors a common etiologic agent. Macerated nodules, cultured in beef infusion broth, yielded Gram-positive green-producing streptococci in 12 out of 17 cases (70.6 per cent).

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Immunization with Bacterial Bodies Against Tetanus.—In a further study, COLEMAN with GUNNISON (*Am. J. Hyg.*, 1931, 14, 526) states that during the World War Tulloch showed by the agglutination reaction that *Cl. tetani* could be differentiated into 4 serologic types which have since been extended to 9 by other workers. Tulloch investigated several phases of the question of type specificity and attempted to correlate his results with his clinical observations, his idea being that perhaps serums of greater prophylactic value could be produced if bacterial bodies as well as filtered toxin were used in the immunization of animals. These experiments were "suggestive" but very inconclusive. It has been reported by workers in China that antispore and antibacterial serums "practically free from antitoxin" which have type specific protective value against infection with *Cl. tetani* may be produced in rabbits. Confirmation of this conclusion has not been possible. The present authors were not able to produce by any method serum with bacteria or spores in rabbits, goats or guinea pigs which contained antibacterial or antispore substances or antibodies effective in preventing tetanus infection in guinea pigs. None of these serums enhanced the protective value of purely antitoxic serums. Antitoxic serums produced with the organisms of *Cl. tetani* as well as with toxoid are no more effective in preventing or delaying infection than those produced with filtered toxoid or toxin alone, the unitage in each case being approximately the same.

Mosquitoes Transported by Airplanes.—STAINING METHOD USED IN DETERMINING THEIR IMPORTATION.—GRIFFITTS and GRIFFITTS (*Pub. Health Rep.*, 1931, 46, 2775), by means of observations under experiment and under natural conditions, arrive at the following conclusions: That certain types of airplanes carry mosquitoes (particularly *Aedes ægypti* and *Culex quinquefasciatus*) has been proved. With conditions at airports such as would permit of many mosquitoes getting

aboard, it might be expected that approximately one-fifth of the original number would be transported for a long distance—at least 1250 miles—in 1 day, with repeated landing and the opening of doors, hatches and windows and refueling, unloading and loading taking place. Under average natural mosquito production conditions about airports, heavy infestation of aircraft (like the “loading” of planes in these experiments) would not be expected and, consequently, mosquitoes in only small numbers would make the trip. However, even one infected, or infective, *Aedes ægypti* might be the means of starting an epidemic. Notwithstanding the fact that airplanes may, or do, transport mosquitoes, this mode of introduction of mosquito-borne disease is probably secondary in importance to the importation of infected man. With the relatively small number of mosquitoes carried by aircraft and the facility with which airplanes may be freed from mosquitoes at ports of departure, it may safely be concluded that, while there is a recognized potential danger, there is no obstacle to the efficient treatment of airplanes so as to destroy mosquitoes and avoid retardation of air traffic progress.

Case Fatality of Communicable Disease.—WOOD (*J. Prev. Med.*, 1932, 6, 87) states that case-fatality ratios are the proportion of deaths which actually occur in a known number of cases of any disease, that is, the number of cases per death. Case-fatality ratios indicate the completeness of reporting of a disease and show the virulence of the disease. Correct case-fatality ratios depend upon complete reporting and the determined actual number of deaths among the persons whose cases have been reported. Correct ratios cannot be computed from the usual vital statistics tabulations. The following case-fatality ratios are approximately correct: diphtheria, 15 to 19 cases to 1 death; measles, 500 to 1; scarlet fever, 100 to 1; typhoid fever, 8 to 12 cases to 1 death; whooping cough, 125 to 150 cases to 1 death. Any state whose ratio of reported cases to recorded deaths falls much below those figures is obtaining very incomplete reporting, and therefore incomplete control over its quarantinable diseases.

Vaccine in the Prevention of the Common Cold. An Experiment.—BROWN (*Am. J. Hyg.*, 1932, 15, 36) claims that the statistical results of the experiment show little, if any, improvement as regards common colds in the experimental group as a whole compared with the control group. Individuals in the experimental group appear to have received some benefit. This is in accord with the findings that the group as a whole was not completely desensitized to the particular antigens used. Better results may be possible with an increased dosage of the vaccine or by employing with each individual the particular antigens to which he may be shown sensitive.

Syphilis.—PARRAN (*Am. J. Pub. Health*, 1932, 22, 141) considers syphilis from the point of view of the epidemiologist. He states that epidemiologic evidence argues for the practicability of control and eradication through direct public health action. Syphilis appears to spread chiefly through a series of localized outbreaks which can be traced to comparatively few determinable sources; the bulk of infection in the white race is concentrated in the cities; most of the cases have a

limited period of infectivity, and elimination of infectious sources will have a cumulative effect on the trend. The existence of an unknown percentage of subclinical cases, many of which are infectious, does not, in the opinion of the author, invalidate the major conclusion. A large proportion of cases are acquired from untreated and inadequately treated cases. These can be recognized by clinical examination and serologic tests and can be made noninfectious by treatment. By these available methods it seems practicable to eradicate syphilis as a public health problem. CRABTREE and BISHOP (*Ibid.*, p. 157) have made a Wassermann survey of a group of negro families in Tipton County, Tenn. Of a total of 2323 individuals of all ages tested, 602, or 26 per cent, were found to have positive Wassermans; 86.6 per cent of these were between the ages of 15 and 50 years. Of 562 cases placed under treatment and observation, 62 were classed as congenital and 464 as acquired syphilis. When persons are infected with syphilis the likelihood that it will not be apparent to females is 1.8 times that of it not being known to males. Of 195 cases giving a history of known primary lesion, 18.5 per cent cent stated that the lesion was acquired within the past year. Data collected allowed for the estimation that the annual morbidity rate for cases of acquired syphilis in Tipton County, Tenn., is approximately 4233 per 100,000 population. Treatment of cases is shown to be wholly inadequate. The likelihood of a pregnancy resulting in either a stillbirth or miscarriage when either parent has a positive Wassermann is 8.2 times that of such an occurrence when neither parent has a positive Wassermann.

Study in the Epidemiology of Diphtheria in Relation to the Active Immunization of Certain Age Groups.—GODFREY (*Am. J. Pub. Health*, 1932, 22, 237) states that the injection of 50 to 70 per cent of children over 5 years of age with 3 doses of toxin-antitoxin has failed in numerous instances to produce any marked effect on the diphtheria incidence of a community. The immunization of 30 per cent or more of children of the under 5-year age group in addition to more than 50 per cent of children 5 to 9 years has in several instances produced an immediate and striking decline in the diphtheria rate of the community as a whole. The promptness of this seeming response suggests that a high degree of immunity is quickly acquired by a majority of those given 3 doses of toxin-antitoxin. It is a matter probably of a few weeks rather than several months. The point is worthy of further investigation. In only 2 instances known to the writer has a community that had attained 30 per cent immunization of its under 5-year age group suffered even a moderate epidemic. It is possible that immunization of the under 5-year age group should not be uniformly distributed through the community, but should be largely concentrated in sections of highest prevalence if diphtheria is prevalent; if not, then in the congested areas. The present study is given as a working hypothesis, worthy of trial as a means of quickly ridding a community of epidemic diphtheria. Much more data from more varied sources are necessary to establish its validity. To this end uniformity in the tabulation of immunization statistics is a necessity. The Committee on Administrative Practice and all health departments should adopt the standard age grouping in their tables, should classify immunizations by single years of age up to

10 years and should annually or oftener so tabulate their material as to show the present status. It is suggested that the unrecognized case rather than the healthy carrier is responsible for the occult infections occurring epidemics or periods of high prevalence. It seems not improbable that many mild nasal cases would be discovered if diligently sought. Such cases are the ones most likely to spread infection. Finally it should be clearly understood that this presentment is in no sense a plea for any community to stop work when it has attained a 30 per cent immunity. That figure may be much too low. Active immunization, like antitoxin, was introduced on a wholesale scale during a period when diphtheria was receding from a period of high epidemicity. It is, therefore, the more difficult to measure its effect. The immunity conferred may not suffice for an organism of greater invasiveness, virulence and pathogenicity. In any event, the only reasonably sure protection for the individual is individual immunization. The one unvaccinated individual in the city may be the gas station man who serves an itinerant smallpox case. The one infected mosquito may bite a susceptible.

A Further Study of Brucella Infection in Iowa.—HARDY and his associates (*U. S. Pub. Health Rep.*, 1932, 47, 187) report a total of 156 cases of undulant fever in Iowa on the basis of the agglutination reaction. The graver forms of the disease are rare, and the disease is not regarded as an important health hazard. Cases generally were sporadic though 3 cases were traced to one herd and 2 to another. Farmers and farmers' wives contributed about one-half of the cases with the remainder scattered in different groups of the population. As is usually true, males greatly outnumbered females among those infected. There was no case below the age of 10 years. Hogs and cattle are of about equal importance as sources of infection. The patients infected from hogs suffer a more severe form of infection than those infected from cattle. In 3 cases *Brucella melitensis*, variety *abortus*, were isolated from the human case and from the animal suspected of being the source of the disease.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 17, 1932.

The Oxidation of Cystin in a Nonaqueous System.—GERRIT TOENNIES and THEODORE F. LAVINE (Lankenau Research Institute, Philadelphia). Of the 7 theoretically possible compounds, 2 acids and 5 anhydrides, that are, according to the state of oxidation of sulphur, intermediate between cystin and cysteic acid, none has been isolated as yet. The authors attempted to devise a method by which some of these compounds could be prepared. Since oxidation in aqueous medium seems

to involve splitting of the -S-S- linkage and formation of cysteic acid as a consequence, it was attempted to dissolve and oxidize cystin in a nonaqueous and nonalcoholic medium, in order to avert splitting of the sulphur linkage. Intending to avoid the necessity of obtaining the desired solubility in a nonaqueous medium by a change of the molecule by substitution, the authors studied the formation and solubility of salts of cystin in the absence of water. It was found that cystin dissolves easily in a methylalcoholic 1 N HCl solution and that the specific rotation in such a solution is little different from that of an aqueous HCl solution of the same concentration. In the alcoholic solution, however, esterification takes place on standing. A satisfactory system was found in an anhydrous solution of perchloric acid in acetonitrile. A solution of 70 per cent aqueous perchloric acid in acetonitrile is made anhydrous by addition of an amount of acetic anhydrid equivalent to the water present. In this medium perchloric acid dissolves an equivalent amount of cystin and the $\frac{N}{10}$ solution appears stable for at least 4 weeks. Cystin, when oxidized in such a solution by benzoylhydroperoxid at low temperatures, takes up a maximum of 4 oxygen and a precipitate is obtained which is not uniform in composition but approaches the formula $2 R-SO_2-SO_2-R + 1 HClO_4$. This product is extremely hygroscopic and the acidity of its aqueous solution increases rapidly with time, approaching 1 acid for each sulphur. The aqueous solution is capable of reducing iodine as well as of oxidizing potassium iodid. While the nitroprussid test for -SH groups is not produced by the compound in presence of cyanid, a strong test is given if subsequent to the action of iodid, which is oxidized to iodine, cyanid is applied.

A Study of the Nonfermentable Fraction of "Blood Sugar."—F. M. KERN and L. S. SMELO (Department of Physiological Chemistry, University of Pennsylvania). It has been known for some years that the total reducing power of blood, as measured by the reduction of alkaline copper solutions, represents other substances besides "true" sugar. The nonsugar reducing substances ("saccharoid") may be distinguished from the sugar, since they are not fermentable by yeast. Under certain conditions (such as high blood sugar) the indirect technique of Somogyi for the determination of the "saccharoid" was unreliable. Excellent results were obtained when the "residual reduction" was determined directly, using the Shaffer-Hartmann reagent (modified by Somogyi) and filtrates obtained by the Folin-Wu technique from blood which had stood in contact with a washed, active yeast suspension.

The quantity of "saccharoid" in dogs' blood was found to be 27 mg. (± 6 mg.) per 100 cc., while in cats' blood it had an average value of 32 mg. These figures are practically identical with that usually accepted for human blood. This value has been found to be practically independent of variations in diet, which have included meat exclusively (for 28 days), high protein (for 50 days), low protein-high carbohydrate (for 21 days), and a mixed hospital regimen (30 days).

It was not possible to demonstrate a diurnal variation in the saccharoid content of blood. The administration of insulin and adrenalin produced the usual changes in total reducing substances, but the

"saccharoid" remained unchanged in quantity. Fasting (for 72 to 96 hours) is the only experimental condition thus far encountered which appears to have caused a change (slight diminution) in the value of the "saccharoid."

Acute Experimental Glomerulitis.—NEIL McLEOD and GEORGE G. FINNEY (Medical Clinic, School of Medicine, Johns Hopkins University, Baltimore). Focal, scattered glomerular lesions and more diffuse changes involving glomeruli, tubules and interstitial tissue were produced by injection of heated suspensions of green streptococci into the left renal artery of rabbits. The uninjected right kidney served as a control and proved to be normal in every case. Lesions were produced in 16 per cent of 24 normal rabbits and in 45 per cent of 33 animals which had been rendered skin-hypersensitive by repeated intracutaneous injections of green streptococci. In the "sensitized" group the development of glomerulitis bore no relation to the degree of skin sensitivity, to the presence of a secondary skin reaction, or to a specific eye reaction. Of four strains of green streptococcus used, two produced renal lesions more readily than did the others. Glomerular changes included epithelial and endothelial cell proliferation, crescent formation, cellular exudate, fibrin deposits. It is suggested that this glomerulitis is not a reflection of an allergic state.

Tumors in Frogs.—B. LUCKÉ (Laboratory of Pathology, University of Pennsylvania). This preliminary report is based upon a study of 18 frogs (*R. pipiens*) with renal tumors. The tumors were generally located in both kidneys, and appeared as whitish nodules. Histologically they corresponded with adenocarcinomas. The nature of this neoplastic disease is being investigated.

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